ARCHIVES OF PATHOLOGY

VOLUME 39 FEBRUARY 1945 NUMBER 2

COPYRIGHT, 1945, BY THE AMERICAN MEDICAL ASSOCIATION

CONGENITAL GLYCOGENIC TUMORS OF THE HEART

THOMAS M. BATCHELOR, B.S., AND MARK E. MAUN, M.D.

DETROIT

Congenital tumors of the heart, rhabdomyomas, are comparatively rare. Since von Recklinghausen[1] described the first case in 1862, 63 authentic cases have been recorded. One atypical case was reported by Brown and Gray.[2] Four cases have been reported in other species, 1 in a guinea pig by Hueper,[3] 2 in swine by Hieronymi and Kukla[4] and Clausen,[5] and 1 in a bovine animal by Pires and Mucciolo.[6]

Knox and Schorer[7] were the first to record a case in American literature. Since that time cases have been reported by Wolbach,[8] Farber,[9] Yater,[10] Ill and Gray,[11] Wegman and Egbert,[12] Hueper,[13] Labate,[14] Olsen and Cooper[15] and Hillman.[16] The case reported here is the eleventh in American literature and the sixty-third in general medical literature.

REPORT OF A CASE

The mother of the patient was a 19 year old primipara. She was admitted to the hospital Nov. 24, 1943. The last menstrual period was Feb. 25, 1943; the expected date of confinement, Dec. 1, 1943. The prenatal and the past history were noncontributory. The blood pressure was 180 systolic and 124 diastolic. The urine contained albumin (4 plus). The hemoglobin content was 10.5 Gm. (66 per cent); the red cell count was 4,100,000; the white cell count, 11,000 with 72 per cent polymorphonuclear leukocytes. The Kahn test was negative.

On Nov. 25, 1943 the mother spontaneously delivered an apparently normal full term boy, weighing 4 pounds 10¾ ounces (2,119 Gm.). Respirations were slightly delayed; hence oxygen was given, with good results. Three days later the infant suddenly began to show intermittent cyanosis, which, however, soon became permanent and generalized. The heart sounds were normal. Loud moist rales were heard throughout both lungs. The infant pursued a rapidly downhill course and died November 28.

Necropsy.—The autopsy was performed twenty hours after the patient died. The body was that of a white boy 53 cm. in length and approximately 5 pounds (2,268 Gm.) in weight. It was fairly well nourished, and development was good. Slight postmortem rigidity was present. Generalized patchy cyanosis of the skin was seen. No external anomalies were noted.

The bowel surfaces were smooth and shiny. About 50 cc. of serous fluid was present in the peritoneal cavity. The liver weighed 65 Gm., was deep red and soft in consistency. Cut section revealed a marked excess of blood.

The lungs were free of adhesions. No fluid was present in the pleural cavities. Each lung weighed 20 Gm. Crepitation was diminished throughout, and the cut surfaces were moist and deep red.

The spleen weighed 8 Gm. Its cut surface revealed moderate congestion. Each kidney weighed 15 Gm. The organs were moderately soft in consistency, and their cut surfaces were deep red. No tumors or cysts were seen. The gastrointestinal tract showed no abnormalities. Unfortunately the brain was not examined.

The pericardial sac contained 5 cc. of clear straw-colored fluid.

The heart measured 7.5 cm. in width and was engorged with blood. When emptied, the heart with the roots of the great vessels weighed 32 Gm. Beneath the shiny visceral epicardium in the walls of the right and left ventricles were numerous raised, rounded tumor nodules, measuring 2 mm. to 2 cm. in diameter. Beneath the endocardium of the left ventricle there was a raised nodule, measuring 1.5 cm. by 5 mm., that covered the interventricular septum. In the right ventricle two raised nodules, measuring 1 cm. in diameter, were seen beneath the endocardium of the septum. The papillary muscles in both ventricles showed small nodules, about 2 mm. in diameter. Similar nodules were seen in both auricles.

On cut section the nodules were fairly well defined but nonencapsulated; they were subepicardial, intramural and subendocardial in location. Their cut sur-

From the Department of Pathology of Wayne University College of Medicine and St. Mary's Hospital.

1. von Recklinghausen: Monatschr. f. Geburtsch. u. Frauenkr. **20**:1, 1862.

2. Brown, G., and Gray, J.: Lancet **1**:915, 1930.

3. Hueper, W. C.: Am. J. Path. **17**:121, 1941.

4. Hieronymi, E., and Kukla, R.: Virchows Arch. f. path. Anat. **232**:459, 1921.

5. Clausen, L.: Deutsche tierärztl. Wchnschr. **46**: 838, 1938.

6. Pires, E. R., and Mucciolo, P.: Rev. Fac. Med. Vet. Univ. São Paulo **1**:67, 1939.

7. Knox, J. H. M., and Schorer, E. H.: Arch. Pediat. **23**:561, 1906.

8. Wolbach, S. B.: J. M. Research **16**:495, 1907.

9. Farber, S.: Am. J. Path. **7**:105, 1931.

10. Yater, W. M.: Arch. Int. Med. **48**:627, 1931.

11. Ill, C. H., and Gray, F. W.: Am. J. Obst. & Gynec. **28**:264, 1934.

12. Wegman, M. E., and Egbert, D. S.: J. Pediat. **6**:818, 1935.

13. Hueper, W. C.: Arch. Path. **19**:372, 1935.

14. Labate, J. S.: Am. J. Path. **15**:137, 1939.

15. Olsen, R., and Cooper, R. J.: Am. J. Path. **17**: 125, 1941.

16. Hillman, R. W.: Brooklyn Hosp. J. **3**:181, 1941.

faces were yellowish white, smooth and somewhat softer in consistency than the adjacent brownish red myocardium. The valve leaflets were normal in appearance. A patent foramen ovale, measuring 1 cm. in diameter, was present, and a ductus arteriosus, measuring 3 mm. in diameter, connected the pulmonary artery with the aorta.

The heart was immediately placed in a 4 per cent solution of formaldehyde, but it was removed two hours later, and blocks of tissue were placed in absolute alcohol, in Zenker's solution and in a 4 per cent solution of formaldehyde-fixed tissue from the heart were stained with sudan III.

Microscopic Examination.—Sections of the nodules stained with hematoxylin-eosin presented the typical vacuolated appearance described in the literature. The nodules were 500 microns to 2 cm. in diameter. They appeared discrete because of the numerous clear spaces within the cells of the tumors that were in contrast to the more compact eosin-staining cytoplasm of the surrounding myocardial fibers. The boundaries of the nodules for the most part were sharp,

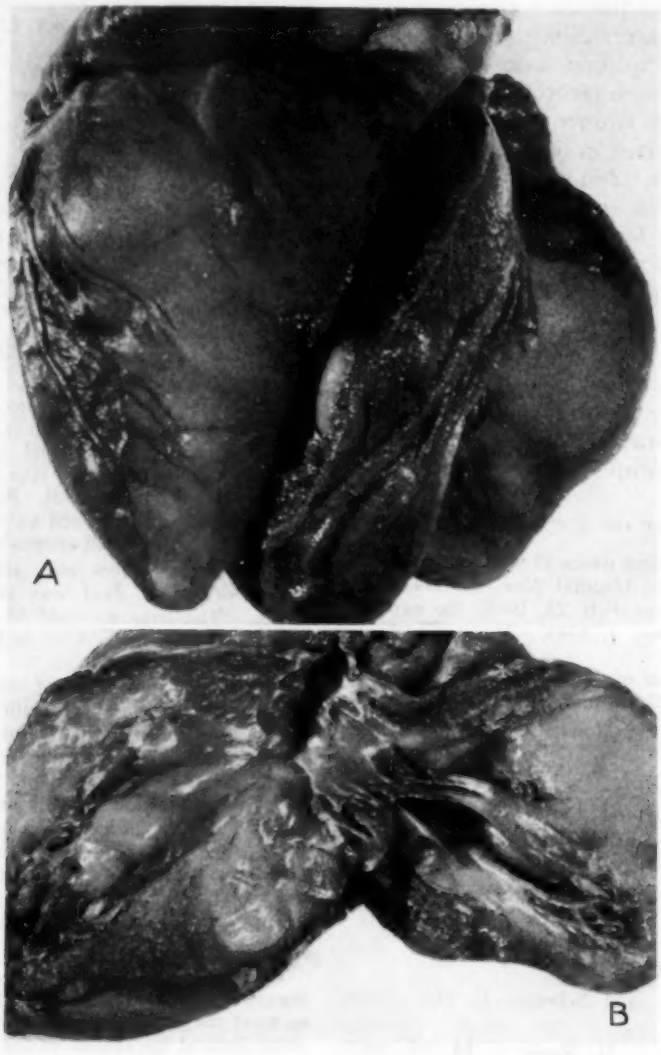


Fig. 1.—*A*, heart with raised tumor nodules of varying sizes protruding from beneath the epicardium of the right ventricle. Nodules may be seen within the myocardium of the open portions of the heart. *B*, left ventricle opened to show raised subendocardial nodule located in the interventricular septum. Other tumors are seen within the myocardium.

maldehyde. Blocks of all the tissues were embedded in paraffin and stained with hematoxylin-eosin. In addition, prepared sections of the heart were stained with azocarmine and with phosphotungstic acid–hematoxylin. Other sections of the heart that were fixed in absolute alcohol and embedded in celloidin (a concentrated preparation of pyroxylin) were cut and stained with Best's carmine stain for glycogen. Frozen sections of formal-

but in some areas a gradual transition from normal cardiac fibers to the vacuolated cells was apparent. A few blood vessels were seen within the tumors. Sections of the tumors stained with hematoxylin-eosin revealed under higher magnification that the nodules were composed of closely packed cells ranging from 8 to 300 microns in diameter. The cells contained large empty spaces with only a small

peripheral rim of eosin-staining cytoplasm. The nuclei when present were located chiefly in the peripheral strands of cytoplasm. Occasionally, however, they were located centrally in the vacuolated cells, surrounded by a narrow zone of cytoplasm that extended to the periphery in spider web fashion.

Sections of the myocardium stained by Best's carmine method revealed numerous glycogen granules within the vacuolated spaces of the tumor cells. Some cardiac fibers that appeared normal with routine hematoxylin-eosin stains were also found to contain fine granules of glycogen.

Sections of the myocardium stained with azocarmine revealed a small amount of connective tissue within the vacuolated tumors and in association with the blood vessels. The normal cardiac fibers stained red, and cross striations within the cytoplasm of the fibers were visible. The vacuolated cells of the tumors were completely surrounded by red-staining granular cytoplasm.

With the aid of phosphotungstic acid–hematoxylin stain, the cytoplasmic granules resembled myofibrillar material. Further, in some areas horizontal sections of the peripheral septums of the vacuolated cells were seen as thin sheaths of sarcoplasm with distinct cross striations. From so striking a picture it is easy for one to believe that the granular appearance of the compressed cytoplasm of the tumor cells represents no more than the cut ends of cross striations. No mitotic figures were seen.

When stained with sudan III, sections of the tumors revealed a few fat droplets within the sarcoplasm of the cells rather than within the vacuolated spaces themselves.

Histologic examination of the other organs revealed bronchopneumonia and partial atelectasis of each lung and acute passive congestion of the liver, the spleen and the kidneys. No glycogenic tumor nodules were found in the other organs and tissues examined.

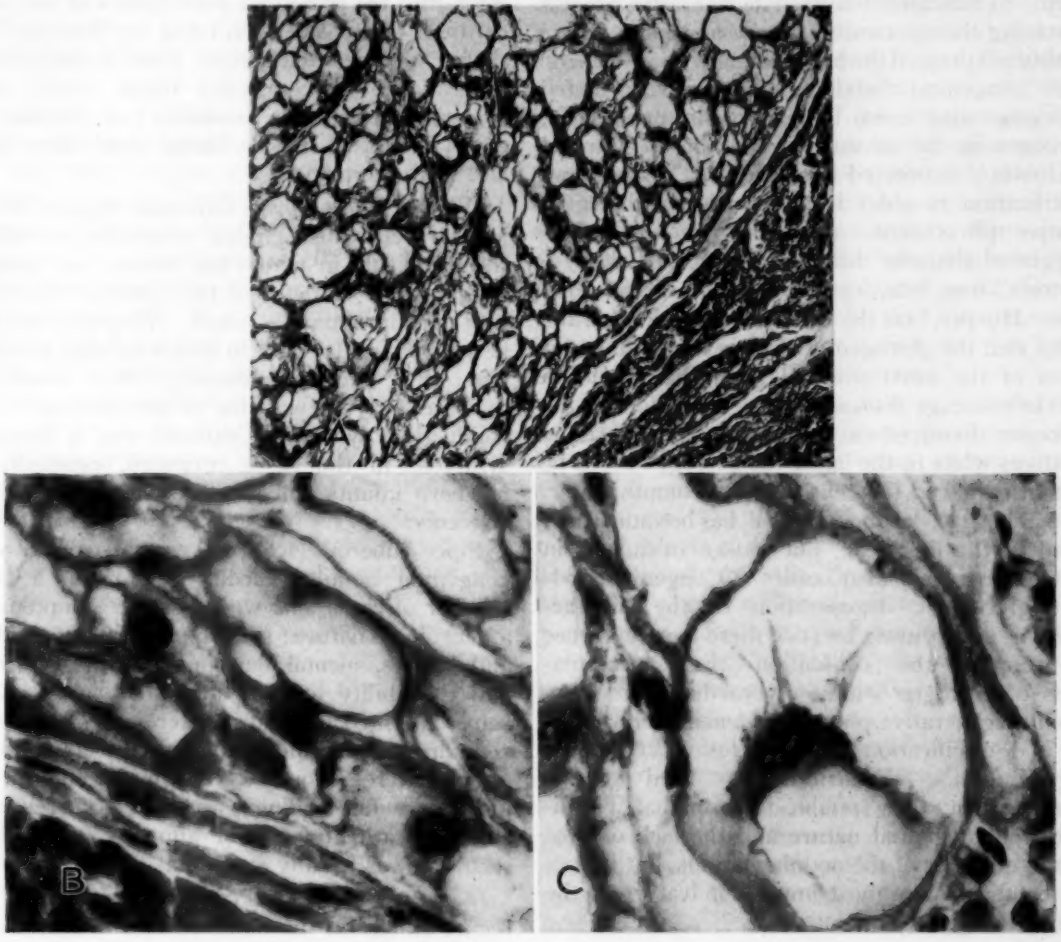


Fig. 2.—*A*, photomicrograph of a nodule and the adjacent normal myocardium. Note marked vacuolation of the tumor cells. Hematoxylin-eosin; × 100. *B*, higher magnification of the edge of the nodule. Note the apparent sharp transition from normal cardiac fibers to vacuolated cells. Hematoxylin-eosin; × 600. *C*, photomicrograph showing a typical spider cell. Note the central location of the nucleus and the delicate cytoplasmic strands having a spider web arrangement. Hematoxylin-eosin; × 600.

COMMENT AND REVIEW OF THE LITERATURE

Terminology.—There has been considerable disagreement over the name that should be attached to the entity under discussion. "Rhabdomyoma" was used by early investigators and has been the term generally accepted by contemporary students of the subject even though they agree that the tumors to which it is attached do not

represent a neoplastic process. Wolbach,[8] using phosphotungstic acid–hematoxylin stain, demonstrated early fibril formation of the cardiac muscle and with this evidence considered the rhabdomyoma a true neoplasm. On the other hand, Steinbiss,[17] Olsen and Cooper,[15] Yater [10] and Hueper [13] endorsed the term "hamartoma" as used by Albrecht,[18] to indicate a tumor-like, nodular, congenital lesion that did not represent a proliferative neoplastic lesion. Olsen and Cooper [15] have offered the term "congenital nodular glycogenic degeneration of the myocardium" to indicate a localized degenerative process involving the myocardium of the newborn. These authors expressed the belief, along with the others, that "congenital rhabdomyomatosis" represented a degenerative lesion because of the presence of glycogen in the vacuolated cells of the tumors. Steinbiss [17] expressed the belief that fibrosis and calcification in older lesions represented degenerative phenomena. Humphreys and Kato [19] suggested that the diffuse type of "rhabdomyomatosis" may be a form of Gierke's storage disease. Hueper,[3] on the other hand, expressed the belief that the glycogen present in the nodular tumors of the heart differed from that found in Gierke's storage disease because in the former the glycogen dissolved out readily in ordinary tissue fixatives while in the latter the glycogen could be demonstrated in the cells weeks to months later. To summarize, "rhabdomyoma" has become firmly fixed in the literature, but it is a misnomer in that no true neoplasm occurs. "Congenital nodular glycogenic degeneration of the myocardium" is not accurate because there is no evidence to support the contention that accumulations of glycogen within myocardial fibers represent degenerative phenomena; neither do fibrosis and calcification in older lesions represent degeneration. "Hamartoma" as used by Albrecht [18] is a more suitable term in that it indicates the congenital nature and the lack of neoplastic qualities of the nodular lesions, but it does not emphasize the most important feature of the entity, the glycogen content.

Origin.—The origin of the nodular glycogenic tumors has been the subject of considerable speculation. Knox and Schorer,[7] Kawamura,[20] Schulgin,[21] Mönckeberg,[22] Abricosoff,[23] Uehlinger [24] and Berger and Vallée [25] expressed the belief that the tumor cells arose from the Purkinje system. However, since lesions could be found in areas where Purkinje fibers were not located, other investigators doubted this theory. Bundschuh [26] and Amersbach and Handorn [27] showed the constituent fibers to be of extra–Purkinje origin. Many observers noted the similarity between the tumor cells and embryonic myocardial fibers. Bundschuh [26] demonstrated that the tumors were composed of a more primitive muscle tissue that was present before differentiation into the two adult constituents of the myocardium occurred. According to Bonome-Cagnetto,[28] degenerated cardiac fibers were replaced in fetal life by connective tissue whose overgrowth caused the isolation of islands of embryonic heart muscle fibers; these fibers gave rise to the tumor cells.

Clinical Symptoms.—Glycogen tumors of the heart rarely cause clinical symptoms except in those patients in whom the tumors are situated on the valve leaflets; in the event of this location murmurs may be heard. Wegman and Egbert [12] reported a case in which cardiac arrhythmia was detected clinically; they concluded that the disorder was due to involvement of the conducting system. Cyanosis was a frequent symptom in the cases reviewed, especially in newborn infants and in those patients who died suddenly.

Since tuberous sclerosis was associated with congenital nodular cardiac tumors in a large number of cases, one would expect symptoms of a neurologic nature; such appeared. In children and infants, mental development was retarded, and the ability to walk and talk was delayed; some exhibited marked indifference to their surroundings. In some of the patients epileptiform attacks were frequent. However, one of the most constant findings was the occurrence of sudden death after minor ailments from which recovery was usually expected.

Incidence.—So-called congenital rhabdomyoma occurs chiefly in the newborn and infants under 1 year of age. In the series studied, totaling 63

17. Steinbiss, W.: Virchows Arch. f. path. Anat. **243**:22, 1923.

18. Albrecht, E.: Verhandl. d. deutsch. path. Gesellsch. **8**:89, 1904.

19. Humphreys, E., and Kato, K.: Am. J. Path. **10**:589, 1934.

20. Kawamura, R.: Centralbl. f. allg. Path. u. path. Anat. **24**:801, 1913.

21. Schulgin, M.: Zentralbl. f. Herz- u. Gefässkr. **5**:33, 1913.

22. Mönckeberg, J. G.: München. med. Wchnschr. **61**:2108, 1914.

23. Abricosoff, A. J.: Beitr. z. path. Anat. u. z. allg. Path. **45**:376, 1909.

24. Uehlinger, E.: Virchows Arch. f. path. Anat. **258**:719, 1925.

25. Berger, L., and Vallée, A.: Ann. d'anat. path. **7**:797, 1930.

26. Bundschuh, E.: Beitr. z. path. Anat. u. z. allg. Path. **54**:278, 1912.

27. Amersbach and Handorn: Frankfurt. Ztschr. f. Path. **25**:124, 1921.

28. Bonome-Cagnetto, A.: Atti d. r. Ist. Veneto di sc., lett. e arti **5**:205, 1903.

cases, the incidence in the various age groups was as follows:

Newborn	15
Under 1 year	18
1 to 3 years	9
3 to 15 years	12
Over 15 years	7
Not given	2
Total	63 cases

The disease affects both males and females but is more common in the former. As for racial distribution, it has been reported in Negroes (Hueper [13] and Yater [10]) and in Japanese (Tamura [29] and Mitani [29a]) as well as in the white race.

Description of Tumors.—Glycogenic tumors involve the left ventricle more frequently than any other site; however, any portion of the heart, including the valve leaflets, may be involved by nodules. The tumors may be subepicardial, intramural or subendocardial. In so-called congenital rhabdomyomatosis one may see any of three pictures. In 11 of the cases reviewed a single tumor was found within the myocardium, usually in the region of the apex of the heart; in 48 of the cases multiple nodules involved almost every portion of the heart, and in 3 cases there was diffuse involvement of the myocardium, the case reported by Schmincke [30] being the most remarkable in that the heart was hypertrophied and the entire myocardium replaced by rhabdomyoma fibers while the normal contour of the heart was retained.

When nodules are seen within the myocardium, they usually appear as discrete, homogeneous, yellowish white areas, somewhat soft in consistency. However, in the case reported by Brown and Gray [2] a single tumor nodule, measuring 3 by 2¼ inches (7.5 to 5.6 cm.) and found in the lateral wall of the left ventricle, presented a pale white cut surface and a distinct coarse fasciculated appearance closely resembling that of a fibroma. Microscopically, the tumor was composed of interlacing bundles of cardiac muscle fibers separated by the abundant connective tissue that formed the bulk of the tumor. Only a few microscopic areas showed slight vacuolation. We feel that this case should not be considered in the same category as the others discussed in this paper because of the absence of typical features described in the cases in the literature and noted in the case we have reported.

Earlier writers were not able to identify definitely the contents of the vacuolated areas or to appreciate their significance. Von Recklinghausen [1] considered the empty spaces to represent lymph or blood channels or "muscle-tubes" of pathologic origin. Virchow [31] thought they were either lymphatic cavities or clear serous spaces. Hlava [32] considered them to be artefacts of fixation. Of the early writers, Ponfick,[33] Knox and Schorer [7] and Wolbach [8] considered them to be intracellular spaces. In regard to the content of the vacuolated spaces Marchand [34] suggested that glycogen might be present because of the similarity of the tumor cells to fetal myocardium. Seiffert [35] was convinced that glycogen was present, although he was unable to demonstrate it clearly. Mönckeberg [22] and Rehder [36] demonstrated glycogen in the tumor cells, and other investigators since then have obtained stains proving that glycogen was present within the vacuoles. Bundschuh [26] found fine droplets of fat in cardiac fibers near the periphery of the vacuolated nodules. Kawamura,[20] Mittasch,[37] Olsen and Cooper [15] and Rae [38] demonstrated fine fat droplets in the cytoplasm of the cardiac fibers. Steinbiss [17] stated definitely that the vacuoles were entirely free from fat, a fact that has been substantiated by later investigators.

Cesaris-Demel [39] was the first to mention the so-called "spider cells" as many-processed cells lying within the vacuolated areas; he considered the spaces to be intercellular. Seiffert [35] compared these "spider cells" to huge embryonic cells. After careful study of the present case, we are convinced that the "spider cell" does not represent a cell within a vacuolated space; it merely represents a striated muscle cell that has become vacuolated by intracellular accumulations of glycogen in such a manner that the nucleus of the cell remains centrally located, surrounded by a narrow zone of cytoplasm, while the remaining cytoplasm assumes a spider web pattern.

Associated Lesions.—Congenital glycogenic tumors of the heart usually occur in association with some other lesions. Von Recklinghausen [1] was the first to note the presence of tuberous sclerosis in cases of rhabdomyoma of the heart,

29. Tamura, O.: Gann **30**:391, 1936.

29a. Mitani, S.: Tr. Soc. path. jap. **24**:589, 1934.

30. Schmincke, A.: Beitr. z. path. Anat. u. z. allg. Path. **70**:513, 1922.

31. Virchow, R.: Virchows Arch. f. path. Anat. **30**: 468; 1864.

32. Hlava, J.: Praze **1**:376, 1887.

33. Ponfick: Verhandl. d. deutsch. path. Gesellsch. **4**:226, 1901.

34. Marchand: Verhandl. d. deutsch. path. Gesellsch. **3**:64, 1901.

35. Seiffert: Verhandl. d. deutsch. path. Gesellsch. **3**:64, 1901.

36. Rehder, H.: Virchows Arch. f. path. Anat. **217**: 174, 1914.

37. Mittasch: München. med. Wchnschr. **69**:571, 1922.

38. Rae, M. V.: Canad. M. A. J. **39**:63, 1938.

39. Cesaris-Demel, A.: Arch. per le sc. med. **19**:139, 1895.

Data on Cases Recorded in the Literature to Date (Enlarged After Farber[9] and Labate[14])

Author	Heart	Glycogen	Brain	Other Organs	Age
1. Von Recklinghausen [1]	Multiple nodules	.....	Tuberous sclerosis	Cutaneous tumor	Newborn
2. Virchow [31]	Multiple nodules	.....	.....	Large liver; tumors of skin	Newborn
3. Hlava [32]	Single nodule	.....	.....	.....	14 days
4. Kolisko, A.: Med. Jahrb. **2**: 135, 1887	Multiple nodules	.....	.....	.....	2 months
5. Cesaris-Demel [33]	Multiple nodules	.....	Tuberous sclerosis	Multiple renal adenoma	3 years
6. Seiffert [35]	Multiple nodules	.....	.....	Cysts of kidney	20 months (M)
7. Seiffert [35]	Multiple nodules	.....	.....	.....	7 months
8. Rothe: Allg. med. Centr.-Ztg. **70**: 175, 1901	Multiple nodules	.....	Tuberous sclerosis	Tumors of breast	.....
9. Ponfick [33]	Multiple nodules	.....	Tuberous sclerosis	.....	7 months
10. Ponfick [33]	Multiple nodules	.....	Tuberous sclerosis	.....	3 years (M)
11. Bonome-Cagnetto [29]	Multiple nodules	.....	Tuberous sclerosis	.....	18 months (F)
12. Riedmatten, R.: Trav. d. l'Inst. path. d. Lausanne **3**: 167, 1904	Multiple nodules	.....	Tuberous sclerosis	.....	7 months
13. Knox and Schorer [7] *	Multiple tumors	.....	.....	.....	7 months
14. Wolbach [8] *	Single tumor	.....	.....	Multiple neuroglioma	10 months (F)
15. Abricosoff [23]	Multiple nodules	Present	Tuberous sclerosis	.....	3¼ years
16. Ehrnrooth, E.: Beitr. z. path. Anat. u. z. allg. Path. **51**: 262, 1911	Single tumor	.....	.....	.....	7 months
17. Bundschuh [26]	Multiple nodules	.....	Tuberous sclerosis	Renal tumors and cysts, tumors of skin	2 years (F)
18. Jonas, W.: Frankfurt. Ztschr. f. Path. **11**: 105, 1912	Multiple nodules	.....	Tuberous sclerosis	Harelip, cleft palate, anomalous kidney	6 months (M)
19. Kawamura [20]	Multiple nodules	.....	.....	Renal tumors, congenital anomalies of pancreas, esophagus, rectum	4 years (F)
20. Schulgin [21]	Multiple nodules	.....	Tuberous sclerosis	Renal tumors	6 days
21. Schulgin [21]	Multiple nodules	.....	Tuberous sclerosis	.....	6 years
22. Rehder [36]	Multiple nodules	Present	.....	.....	Newborn
23. Mönckeberg [22]	Multiple nodules	Present	.....	Absence of right kidney and ureter	14 months
24. Ribbert, H.: Centralbl. f. allg. Path. u. path. Anat. **26**: 241, 1915	Multiple nodules	.....	Tuberous sclerosis	Renal cysts	1 year
25. Hisinger-Jagerskiold, E.: Finska läk.-sällsk. Handl. **58**: 953, 1916	Single tumor	.....	.....	Renal tumors	7½ months
26. Melnikov-Razvedenkov [40]	Single tumor	.....	.....	.....	20-25 years (M)
27. Amersbach and Handorn [27]	Single tumor	.....	.....	.....	7 days (M)
28. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Aerzte, Berlin, W. de Gruyter & Co., 1922	Multiple nodules	.....	Tuberous sclerosis	.....	3 years
29. Kaufmann, E.: Ibid	Multiple nodules	.....	Tuberous sclerosis	Renal tumors	7 years
30. Mittasch [37]	Multiple nodules	.....	Tuberous sclerosis	Renal tumors	4 months
31. Mittasch [37]	Multiple nodules	.....	Tuberous sclerosis	Renal tumors	14 years (M)
32. Mittasch [37]	Multiple nodules	.....	Tuberous sclerosis	Renal tumors, angiomyolipoma of liver	31 years (M)
33. Schmincke [30]	Diffuse involvement	.....	.....	Congenital tumors of lungs	Newborn
34. Steinbiss [17]	Multiple nodules	.....	Tuberous sclerosis	Fibroepithelioma of skin	5 years (M)
35. Steinbiss [17]	Multiple nodules	.....	Tuberous sclerosis	Renal tumors	3 years (M)
36. Steinbiss [17]	Multiple nodules	.....	Tuberous sclerosis	Renal and cutaneous tumors	10 years (M)
37. Steinbiss [17]	Single tumor with cicatrix	.....	Tuberous sclerosis	Renal tumors and cysts	16 years (M)
38. Steinbiss [17]	Multiple nodules	.....	Tuberous sclerosis	Renal tumors	21 years (F)
39. Steinbiss [17]	Single tumor	.....	Tuberous sclerosis	Renal tumors	35 years
40. Omodei-Zorini, A.: Arch. per le sc. med. **46**: 97, 1923	Single tumor	.....	.....	.....	2½ years
41. Uehlinger [24]	Multiple nodules	.....	.....	.....	20 years
42. Sikl [41]	Single nodule	.....	.....	.....	9 weeks (M)
43. Berger and Vallée [25]	Multiple nodules	.....	.....	Renal cysts	2 years
44. Farber [9] *	Multiple nodules	Present	Tuberous sclerosis	Renal cysts	6 months (F)
45. Yater [10] *	Multiple nodules	.....	Tuberous sclerosis	Renal tumor	5 years (F)
46. Reitano, R., and Nucciotti, L.: Cuore e circolaz **17**: 605, 1933	Multiple nodules	.....	.....	.....	1 day
47. Baruchev [42]	Single nodule	.....	.....	.....	3 days
48. Ill and Gray [11] *	Multiple nodules	.....	.....	Hepatomegaly and splenomegaly	48 hours (M)
49. Lymburner [43]	Multiple nodules	.....	.....	.....	45 years (F)
50. Mitani [29a]	Multiple nodules	.....	Tuberous sclerosis	Renal cysts	Newborn (M)
51. Wegman and Egbert [12] *	Multiple nodules	.....	.....	Renal cysts	10 months (F)
52. Hueper [13] *	Multiple foci (microscopic)	Present	Tuberous sclerosis	Renal cysts, hepatomegaly, multiple spongioblastoma of basal ganglions	7 months (M)
53. Pauli, W.: Monatschr. f. Kinderh. **66**: 22, 1936	Diffuse tumor	.....	.....	Hepatomegaly, hydrocele	4 months (M)
54. Pauli, W.: Ibid	Diffuse tumor	.....	.....	.....	6½ months (M)
55. Tamura [29]	.....	.....	.....	.....	.....
56. Eliakis [45]	Multiple nodules	.....	.....	Polycystic kidneys	24 hours (F)
57. O'Flynn and Mackay [44]	Multiple nodules	.....	Tuberous sclerosis	.....	8½ months (M)
58. Rae [38]	Multiple nodules	.....	.....	Hepatomegaly, splenomegaly, partial atelectasis of lungs	3 days (M)
59. Stewart [46]	Multiple nodules	.....	Tuberous sclerosis	Renal cysts	9 months (M)
60. Labate [14] *	Multiple nodules	.....	Tuberous sclerosis	Anomaly of heart	3 hours (M)
61. Hillman [16] *	Multiple nodules	Present	Tuberous sclerosis	.....	21 months (F)
62. Olsen and Cooper [15] *	Multiple nodules	Present	.....	Hypertrophic pyloric stenosis, 4 lobes to right lung, atelectasis of both lungs, renal abscess	40 days (M)
63. Batchelor, T. M., and Maun, M. E.: Arch. Path., this issue *	Multiple nodules	Present	.....	Partial atelectasis of both lungs	3 days (M)

* Cases reported in American literature.

but he failed to describe the lesion. Likewise Cesaris-Demel [39] failed to describe this condition that occurred in association with rhabdomyoma of the heart in the case which he reported. It remained for Ponfick [38] to give a clear description of the associated tuberous sclerosis in his 2 cases of rhabdomyoma. He sought to explain both on a common basis of fetal malnutrition with secondary vascular changes. The tumors in all 6 cases reported by Steinbiss [17] were associated with tuberous sclerosis. In a review of the literature he found that lesions of the brain occurred in 1 of 4 cases in which the heart was involved by a single nodule, in contrast to 24 of 28 cases in which the heart was involved by multiple tumors. Labate,[14] in a comprehensive review of the literature, reported tuberous sclerosis in 29 of 51 cases reviewed. However, in cases not included in the review, namely, those of Melnikov-Razvedenkov,[40] Sikl,[41] Yater,[10] Baruchev,[42] Lymburner,[43] O'Flynn and Mackay,[44] Eliakis,[45] Rae [38] and Stewart,[46] tuberous sclerosis was reported by Yater,[10] O'Flynn and Mackay [44] and Stewart.[46] Since 1939, 2 additional cases, exclusive of the present case, have been added to the literature. Hillman [16] reported tuberous sclerosis. The brain was not examined by Olsen and Cooper.[15]

Although the present review reveals that tuberous sclerosis has been observed in 50 per cent of the cases of congenital nodular glycogenic tumors of the heart, there is no doubt that the incidence of coexistence of the two lesions is much higher. Other congenital disturbances that are frequently seen with these tumors include cysts and tumors of the kidneys, tumors of the sebaceous glands, harelip, cleft palate, multiple glioma of the brain and congenital malformations of the pancreas, the kidneys and the lungs.

SUMMARY

In a case of multiple tumors of the heart in a 3 day old boy glycogen was demonstrated within the tumor cells.

A comprehensive review of the literature on so-called congenital rhabdomyoma of the heart revealed 62 authentic cases of tumors of the heart that presented a characteristic vacuolated appearance on microscopic examination.

The cardiac tumors were seen chiefly in infants and the newborn, with 52 per cent of the patients dying in the first year of life and 86 per cent before they reached puberty.

The clinical symptoms were nonspecific, and in no case was the diagnosis made before death. Frequently the symptoms were due to associated lesions. Tuberous sclerosis was found in 50 per cent of the cases.

We suggest that the term "congenital nodular glycogenic tumors of the heart" should replace "congenital rhabdomyoma" until more is known about the nature of the lesions.

40. Melnikov-Razvedenkov, N. F.: Mosk. M. J. (no. 10) **9**:64, 1929.

41. Sikl, H.: Časop. lék. česk. **64**:757, 1925.

42. Baruchev, S. K.: J. Rann. Detsk. Vozr. **13**:473, 1933.

43. Lymburner, R. M.: Canad. M. A. J. **30**:368, 1934.

44. O'Flynn, E., and Mackay, H.: Proc. Roy. Soc. Med. **30**:1063, 1937.

45. Eliakis, M.: Ann. de méd. lég. **17**:815, 1937.

46. Stewart, T. D.: New Zealand M. J. **39**:63, 1938.

PRIMARY TUMOR OF THE HEART

REUBEN STRAUS, M.D., AND REUBEN MERLISS, M.D.
LOS ANGELES

Reports of primary tumor of the heart appear infrequently in the literature. Because of the reluctance of many students of the subject to accept the diagnosis given in some of these reports, there has been a considerable variation in the estimate of the number of cases that have occurred, the number varying with the bias of the author.

In 1938 Larson and Sheppard [1] accepted 155 cases as sufficiently authentic to be included in an introduction to the report of a case of their own. Since then only 7 more cases have been described.[2] We now add 3 additional ones that were recently encountered at autopsies, 2 on two successive days and the third nine months later.

REPORT OF CASES

CASE 1.—L. L., a 57 year old white man admitted to the Cedars of Lebanon Hospital on Dec. 31, 1943, complained of having had difficulty in breathing, swelling of the ankles and the abdomen and considerable weakness for the preceding five to six months. He asserted that until the onset of his present symptoms he had been completely well and that his symptoms developed gradually and then became progressively worse. He further recalled that three months prior to admission he had become jaundiced for a week, but at no time were acholic stools noted. He complained of a lack of appetite and of a loss of 35 pounds (15.9 Kg.) in weight. Concomitant with the onset of symptoms, he noted a pronounced reduction in urinary output, which persisted. The past history by systems contributed nothing of interest.

The patient appeared moderately cyanotic, tired and weak. The head and neck showed nothing remarkable. The chest revealed fremitus impaired, the percussion note dull and breath sounds suppressed posteriorly at the base of the right lung. A few crepitant rales were heard at the base of the left lung. The heart was normal in size by percussion; the pulse rate was 84 and the blood pressure 118 systolic and 110 diastolic. The cardiac tones were distant, but a rough systolic murmur could be heard over the apex. The peripheral blood vessels were moderately sclerotic. There were moderate ascites and edema of the lower extremities. The venous pressure was 280 mm. of water, and the circulation time with saccharine was nineteen seconds. The rest of the physical examination revealed nothing of importance.

The only significant laboratory findings were a low level of the blood cholesterol (109 mg. per hundred cubic centimeters), slight polycythemia (erythrocytes 5,460,000 per cubic millimeter and hemoglobin of 15.7 Gm. per hundred cubic centimeters), deficient plasma prothrombin time (40 per cent of normal), deficient removal of sulfobromophthalein from the plasma (90 per cent of the dye remaining in the blood one hour after injection), poor excretion of phenolsulfonphthalein (a trace excreted by the kidneys in two hours) and a urine volume of 170 cc. for twelve hours, containing large numbers of leukocytes, erythrocytes, casts and a moderate amount of albumin.

The condition was diagnosed as a hepatorenal syndrome, but the picture was not clear. A thoracentesis of the right side of the chest yielded 1,000 cc. of clear amber fluid.

During his stay in the hospital, the respiratory rate remained between 30 and 40. Cyanosis persisted, only temporarily relieved by oxygen. Terminally the pulse rate, which had been normal, rose to 120. The temperature stayed within normal limits except just before death, when it rose to 102 F. On the fourth hospital day the patient suddenly became markedly cyanotic and pulseless, and died.

Autopsy (about twenty hours after death).—The body was well nourished. There was pronounced cyanosis of the lips and the nail beds. No edema of the lower extremities was noted, but there was moderate edema of the subcutaneous tissue of the torso, as well as about 10 liters of clear serous fluid in the peritoneal sac, 2,000 cc. in the left pleural sac, 500 cc. in the right pleural sac and about 225 cc. in the pericardial sac. The heart weighed 420 Gm. The external aspect presented nothing remarkable. When the heart was opened, the right atrium was considerably dilated. Attached to this aspect of the interatrial septum just posterior to and above the foramen ovale was an ovoid polypoid mass, 10.5 by 6 by 3.5 cm., about one third of which projected into the right ventricle. A smooth glistening membrane covered this mass. It was soft, semitranslucent and mottled yellow, reddish brown and grayish white. On section it presented an extremely fine glistening texture, due in part to edema. The pedicle was short, measuring 1.5 cm. in length. At the point of attachment to the atrium the substance of the stalk blended with the subendocardial stroma. The foramen ovale was patent to a probe along its posterior margin. The endocardium, the valve leaflets and the myocardium presented nothing remarkable except for moderate hypertrophy of the muscularis of the right atrium and ventricle. No mural thrombi were seen.

Microscopic examination of the cardiac tumor revealed a relatively acellular eosinophilic matrix, in

From the Department of Pathology of the Cedars of Lebanon Hospital.

1. Larson, C. P., and Sheppard, J. A.: Arch. Path. **26**:717, 1938.

2. (*a*) Bennett, D. W.; Konigsberg, J., and Dublin, W.: Am. Heart J. **16**:117, 1938. (*b*) Boman, P. G.: Ann. Int. Med. **12**:258, 1938. (*c*) Haythorn, S. R.; Ray, W. B., and Wolff, R. A.: Am. J. Path. **17**:261, 1941. (*d*) Jackson, M. N., and Jacobson, J. N.: Lancet **2**:740, 1939. (*e*) Martin, W. C.; Tuohy, E. L., and Will, C.: Am. Heart J. **17**:728, 1939. (*f*) Reisinger, J. A.; Pekin, T. J., and Blumenthal, B.: Ann. Int. Med. **17**:995, 1942. (*g*) Strouse, S.: Arch. Int. Med. **62**:401, 1938.

part granular and in part hyaline, in which were seen numerous well developed blood vessels and scattered round, spindle and stellate cells. In a few areas there was considerable extracellular and intracellular hemosiderin, the latter within endothelial phagocytes. Mucicarmine stains showed essentially no mucin, only a faint red discoloration being noted in areas, which could have been artefact. With Wilder's reticulum stain sections revealed abundant reticulum.

The walls of the inferior vena cava and of the splenic vein were considerably thickened, reflecting the increased venous pressure noted clinically. The lungs presented moderate congestion, edema and focal atelectasis.

The spleen weighed 300 Gm. and showed considerable chronic passive congestion. The liver weighed 1,940 Gm. and reflected chronic passive congestion of a severe degree. The other organs of the abdominal cavity presented no significant abnormality.

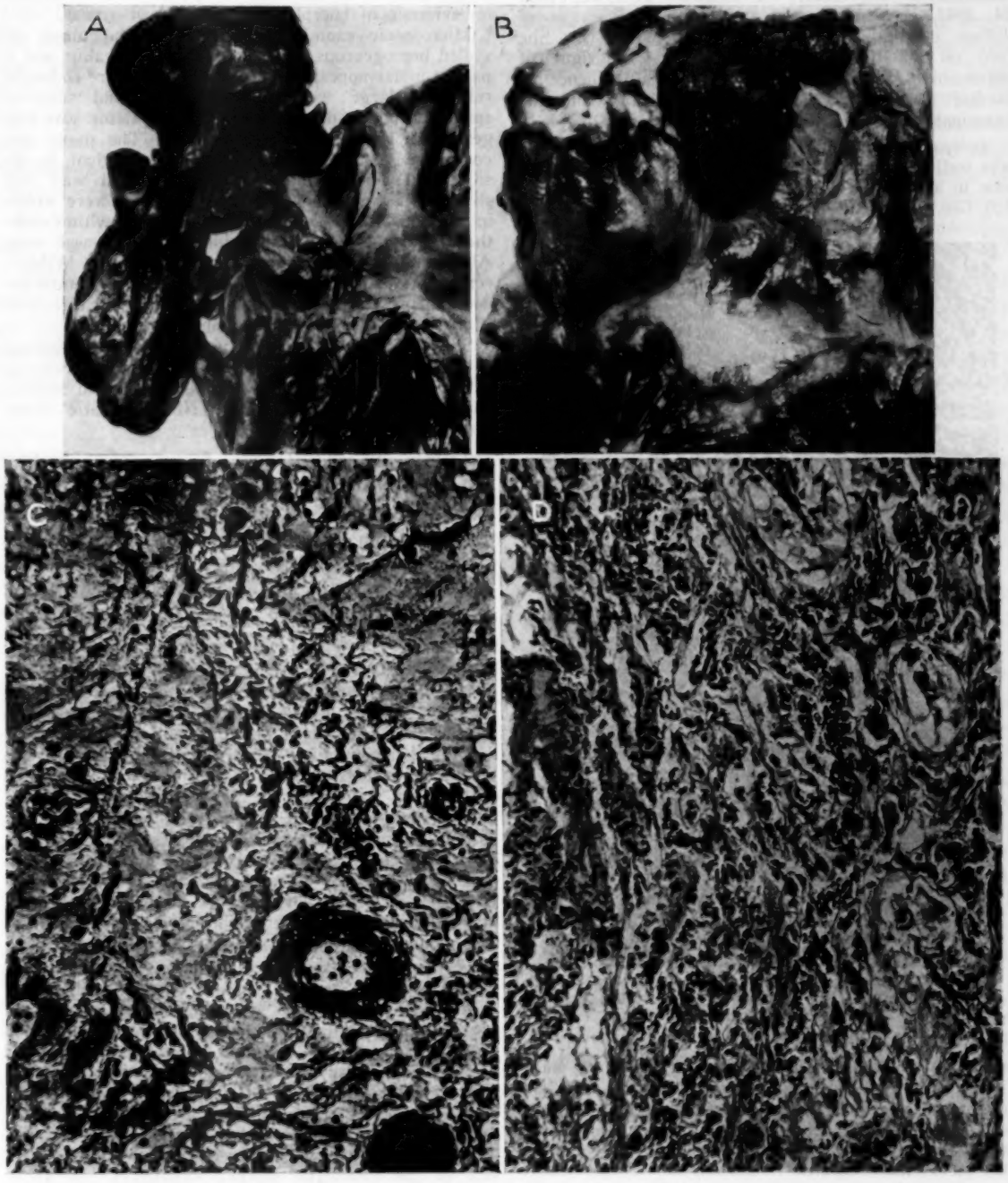


Fig. 1.—*A*, myxoma in case 1 elevated to reveal its attachment to the interatrial septum. *B*, primary myxosarcoma of the left atrium in case 2. *C*, section of the tumor in case 1 (hematoxylin and eosin). *D*, section of the tumor in case 2 (hematoxylin and eosin).

Death in case 1 was due to the cardiac tumor, myxoma, which by a "ball and valve" mechanism

produced marked stenosis of the tricuspid valve with severe cor pulmonale and effusions in the serous cavities of the body.

CASE 2.—E. N., a 62 year old white woman was admitted to the Cedars of Lebanon Hospital, Dec. 24, 1943, in a disoriented state with a diagnosis of diffuse cerebral arteriosclerosis and psychosis. She died on the thirteenth hospital day with signs of pneumonia. Since there was no clinical evidence of cardiac abnormality, details of the history and the examination are omitted.

Autopsy (about nine hours after death).—The body was well nourished. There was no edema and no effusion in any of the serous cavities. The heart weighed 320 Gm. No abnormality was seen on the external

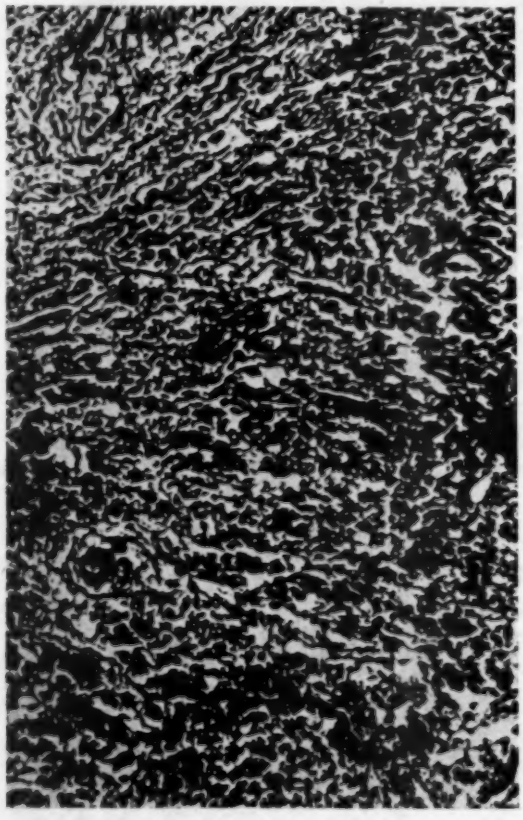


Fig. 2.—Section of the tumor in case 2 with reticulum stain.

aspect. After the heart was opened, a fungating mass with a narrow pedicle was found attached to the left side of the interatrial septum just above the foramen ovale. It measured 5 by 4.5 by 3 cm. It was gelatinous, with hemorrhagic and friable distal portions. The cut surface revealed irregularly distributed white fibrous strands with some areas, chiefly at the base, which were yellow. The myocardium of the septum was not sharply demarcated from the stalk of the tumor. Embedded between the papillary muscle and the columna carneae of the left ventricle were two small gelatinous nodules, the larger 8 mm. in diameter, which resembled the tumor of the atrium. On section superficial invasion of the myocardium could be seen. Except for patency of the foramen ovale along the posterior border, no other abnormality was found in the heart.

The lungs were heavy, considerably congested and edematous with patchy areas of bronchopneumonia in both lower lobes. The other thoracic and abdominal viscera revealed no significant abnormality. The brain weighed 1,220 Gm. There was severe arteriosclerosis of the arteries at the base. Repeated section revealed no evidence of encephalomalacia, old or recent.

Microscopic examination of the arterial tumor revealed homogeneous, translucent, in part hyaline and in part granular appearing matrix in which were embedded relatively large well formed vessels and scattered spindle, round and stellate cells. The tissue was suggestive of mucoid connective tissue. The tumor was considerably more cellular at the base than in the superficial portions but invaded the atrial wall only slightly. Large amounts of hemosiderin were visible in the hemorrhagic areas, some contained within endothelial phagocytes. Stains for mucin showed none. Abundant reticulum was demonstrated with Wilder's reticulum stain. Sections of one of the ventricular nodules presented a strikingly similar structure with slight invasion of one of the papillary muscles.

Sections from the lungs confirmed the gross findings of bronchopneumonia, congestion and edema. Sections of the brain, taken at random, failed to reveal striking variations from the normal. No metastatic tumor nodules could be found.

Death in case 2 was due to the cerebral arteriosclerosis with psychosis and bronchopneumonia. The cardiac tumor, classified as myxosarcoma because of the cellularity at its base, the infiltrative tendency and the implants in the left ventricle, was merely a coincidental finding.

CASE 3.—F. C., a 35 year old white man, was admitted to the Cedars of Lebanon Hospital Aug. 17, 1944. About three weeks earlier, while at work he observed bullous lesions of his hands developing, followed by a generalized pruritic erythematous macular eruption. About two weeks later abdominal cramps and bloody diarrhea made their appearance, associated with nausea and vomiting.

Examination revealed very severe shock, rapid respirations, stupor, abdominal tenderness and distention, and hemorrhagic pleural effusions. Laboratory tests showed evidence of extensive damage of the liver and the kidneys. His course in the hospital was rapidly downhill, death occurring on the third hospital day.

Autopsy (about fourteen hours after death).—The hemorrhagic ulcerative enteritis, the severe cloudy swelling of the liver and the kidneys and the hemorrhage of the skin and the lungs were suggestive of poisoning, probably industrial in origin. Chemical examination revealed only slight amounts of cadmium in these organs. The paralytic ileus with peritonitis and bronchopneumonia were terminal complicating events.

The incidental observation of a tumor of the heart made this organ of special interest. It weighed 380 Gm. The external aspect was not remarkable. On the right side of the interatrial septum, situated 1 cm. above the obliterated foramen ovale was a pedunculated papillary tumor nodule 1 cm. in diameter. The tumor was tan, semitranslucent, with a fine fibrillar structure, and was attached to the endocardium by a thin delicate stalk. The valve leaflets, the endocardium and the myocardium presented no abnormality.

Microscopic examination of the tumor revealed a villus structure covered by a prominent layer of endothelium. The stroma was homogeneous, relatively acellular and hyaline, in places deeply acidophilic and in part lavender. A few scattered small mononuclear

cells could be seen. The lesion was classified as papillary myxoma.

COMMENT

Historically,[3] Boneti in 1700 and Morgagni in 1762 have both been credited with having been the first authors to describe primary tumors of the heart. However, many pathologists believe that Albers in 1835 reported the first authentic case of primary tumor of the heart, fibroma, and that Bodenheimer [4] in 1865 described the first authentic primary sarcoma of the heart. Much of the early difficulty in assigning these credits was due to the inability to distinguish convincingly between a thrombus and a tumor.

Perlstein,[3] Goldstein,[5] Morris,[6] Yater [7] and more recently Strouse [2g] have presented excellent reviews of the entire subject of primary tumor of the heart. Briefly, it is stated that the site of tumor may be in practically any part of the heart but that it is less frequently on a valve and most commonly in an atrium. Apparently the tumor may be either single or multiple. It is agreed that in all cases of tumor of the heart the neoplasm is of mesoblastic origin and therefore it has been reported as myxoma, fibroma, lipoma, lymphangioendothelioma, hemangioendothelioma, leiomyoma, rhabdomyoma, rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma and polymorphous cell sarcoma. According to Yater,[7] the primary cardiac tumor is cancerous in 17.8 per cent of the cases, but more recently Larson and Sheppard [1] calculated the incidence of cancer to be as high as 29 per cent. According to the literature, the disease occurs twice as frequently among males as among females. The younger age group is chiefly affected, but ages have ranged from 10 months [8] to 79 years.[3]

Most authors reporting cases of tumor of the heart fail to make note of the incidence of the primary tumor in their autopsy experience and those who do give widely divergent observations. For instance, Shelburne [9] reports 3 cases of primary cardiac tumor among 1,200 autopsies at Baylor University, an incidence of 0.25 per cent, while Lymburner [8] found 4 cases among 8,550 autopsies at the Mayo Clinic, an incidence of 0.05 per cent. On the other hand, none was observed by Scott and Garvin [10] in 11,000 autopsies at the Cleveland City Hospital, and Pollia and Gogol [11] encountered not a single instance of cardiac tumor in the 12,000 autopsies at the Los Angeles County Hospital up to 1936. To date, practically 30,000 autopsies have been made at the last-named institution with the same negative experience. At the Cedars of Lebanon Hospital, approximately 1,550 autopsies have been made to date, in 3 of which primary tumor of the heart was observed, giving an incidence of 0.19 per cent. This wide variation would suggest that perhaps estimates of the incidence of this disease are erroneous for lack of a sufficient number of cases. From 1938 to 1942, according to statistics of the American Medical Association,[11] there were 480,331 autopsies in the United States. During this period 8 cases of primary cardiac tumor were reported. If it could be assumed that all such cases noted at autopsy were reported, and from the unusual nature of the lesion it appears quite likely they would be, the incidence would be 0.0017 per cent, which seems more consistent with the rarity of the lesion. This makes the occurrence of 3 instances of this rare condition at one institution within a short time (2 on consecutive days and 1 nine months later) a striking coincidence.

As a rule, tumor of the heart is not diagnosed clinically. In patients, who have a primary cancer elsewhere and subsequently show signs of cardiac irregularity, metastatic tumor of the heart has been diagnosed. On the other hand, there are many cases of metastatic tumor of the heart that present no electrocardiographic or clinical signs.[10] How such experience may lead to inaccurate though logical diagnosis is exemplified in a case reported by Beck and Thatcher [12]: Biopsy of metastatic tumors of the skin revealed spindle cell sarcoma. Later, when abnormal cardiac manifestations were noted, a diagnosis of metastatic sarcoma of the heart was made. At autopsy this was found to be primary sarcoma of the heart with generalized metastases.

Only 2 cases are recorded in which primary tumor of the heart was diagnosed before death. Shelburne [9a] cited Goettel [13] as having credited Pavlowsky [14] with being the first to make such a clinical diagnosis. However, Strouse, on reviewing Pavlowsky's original article, reported the citation to be erroneous. In Pavlowsky's case a correlation between the clinical and the postmortem observations was made only after a peduncu-

3. Perlstein, L.: Am. J. M. Sc. **156**:214, 1918.
4. Bodenheimer, cited by Larson and Sheppard.[1]
5. Goldstein, H. I.: New York M. J. **115**:97 and 158, 1922.
6. Morris, L. M.: Am. Heart J. **3**:219, 1927.
7. Yater, W. M.: Arch. Int. Med. **48**:627, 1931.
8. Lymburner, R. M.: Canad. M. A. J. **30**:368, 1934.
9. Shelburne, S. A.: (*a*) Ann. Int. Med. **9**:340, 1935; (*b*) Texas State J. Med. **31**:433, 1935.
10. Scott, R. W., and Garvin, C. F.: Am. Heart J. **17**:431, 1939.
11. Pollia, J. A., and Gogol, L. J.: Am. J. Cancer **27**:329, 1936.
12. Beck, C. S., and Thatcher, H. S.: Arch. Int. Med. **36**:830, 1925.
13. Goettel, L.: Deutsche med. Wchnschr. **45**:937, 1919.
14. Pavlowsky, R.: Berl. klin. Wchnschr. **32**:393, 1895.

lated benign tumor of the right atrium with stenosis of the tricuspid valve was demonstrated at autopsy.

Barnes and co-workers [15] in 1934 reported the case of a 62 year old woman in which a diagnosis of primary sarcoma of the heart was made tentatively during life from the finding of a hemorrhagic pericardial effusion, an electrocardiogram showing interference with the conduction system of the heart and a biopsy of a nodule in the shoulder girdle, diagnosed as metastatic sarcoma. At autopsy their contention was verified by the observation of a tumor which involved the right ventricle and auricle, diagnosed as rhabdomyosarcoma.

Shelburne [9a] deserves praise for the scholarly analysis that is contained in his case report. His patient, a 24 year old Negro man, complained of abdominal pain, distention, fainting spells and cough and presented signs of right-sided cardiac failure of sudden onset and pericardial effusion. The diagnosis of primary tumor of the heart was based on (1) signs of cardiac decompensation, (2) presence of a serosanguineous pericardial effusion as shown by pericardial tap, with rapid recurrence, (3) absence of signs or symptoms of tuberculosis or syphilis, (4) absence of signs of cancer elsewhere, (5) exclusion of rheumatic fever and other infections by the nature of the fluid and the absence of fever and (6) exclusion of rupture of a cardiac aneurysm or a coronary vessel by a comparison of the erythrocyte count of the pericardial fluid with that of the peripheral blood. After his diagnosis was recorded, an electrocardiogram revealed a bundle branch block. At autopsy a tumor was found in the left atrium, infiltrating the atrioventricular septum half way to the apex of the heart, diagnosed as spindle cell sarcoma.

Whether or not primary tumor of the heart can be diagnosed prior to death will depend certainly on its ability to produce symptoms by interfering with the cardiac mechanism. A small, slowly growing tumor of a chamber of the heart, and in some cases a larger one in an "out of the way" position, would not be physiologically apparent. A tumor on a valve, if sufficiently large, could be expected to produce murmurs but, unless thought of, would certainly be overlooked in the differential diagnosis. A large tumor of an atrium with a ball and valve action in either the mitral or the tricuspid ring and with murmurs affected by a shift in the position of the body should certainly be amenable to clinical diagnosis if kept in mind. In regard to cancer, the signs and symptoms most likely to be produced would be hemorrhagic pericardial effusions due to pericardial involvement, interference with the conduction system from an infiltration of the myocardium, murmurs when the valves are involved, and if the tumor is friable, distant metastases and possibly emboli. At times the roentgenogram may be of assistance, particularly when a large bulky tumor produces gross changes in the shape of the heart or an intravenously injected radio-opaque dye outlines the chambers of the heart. All cardiac tumors are usually characterized clinically by a sudden onset of severe cardiac failure without any apparent etiologic or anatomic basis, and a fairly rapid downhill course. Strouse's case [2g] of forty-three years' duration is the longest on record.

15. Barnes, A. R.; Beaver, D. C., and Snell, A. M.: Am. Heart J. **9**:480, 1934.

SUMMARY

Primary tumor of the heart occurs infrequently. Only 163 cases have been reported to date. Individual experience varies considerably, since some whose experience included as many as 30,000 autopsies have seen none whereas others have reported 3 cases of primary cardiac tumor among 1,200 autopsies. When the 8 cases of cardiac tumor reported from 1938 to 1942 in this country are viewed against the background of the national autopsy experience of 480,331 cases reported by the American Medical Association,[16] the incidence of primary tumor of the heart is 0.0017 per cent, assuming all cases to have been reported.

Of the 3 additional cases of primary tumor of the heart herewith reported, 2 were instances of myxoma and 1 was a case of myxosarcoma. In 2 the tumor was silent, in the third it produced clinical signs and symptoms of tricuspid stenosis.

As a rule, primary tumor of the heart is clinically silent. Only 2 cases are on record which were diagnosed prior to death. In both the tumor was a cancer involving the conduction system and in both there was a hemorrhagic pericardial effusion. In no case of benign tumor has the diagnosis been made before death.

The sudden onset of signs of cardiac decompensation in a young person without a preexisting history of cardiac disease, with no discoverable anatomic basis for the cardiac disease, a hemorrhagic pericardial effusion, sometimes an involvement of valvular function or of the conduction system and signs of valvular stenosis which change on motion of the body, as well as signs of mediastinal tumor with alteration of the appearance of the shape of the heart in the roentgenogram, should cause one to consider primary tumor of the heart in the differential diagnosis of the condition under examination.

16. Necropsy Performance in Internship Hospitals, J. A. M. A. **110**:974, 1938; **112**:924, 1939; **114**:1171, 1940; **116**:1068, 1940; **118**:1065, 1942; **120**:852, 1943.

ESOPHAGEAL CARCINOMA IN BRITISH WEST INDIAN AND PANAMANIAN NEGROES

A STUDY OF THE INCIDENCE, ETIOLOGIC FACTORS AND PATHOLOGIC ANATOMY IN FIFTY CASES

MAJOR WRAY J. TOMLINSON

AND

FIRST LIEUTENANT LESTER A. WILSON JR.

MEDICAL CORPS, ARMY OF THE UNITED STATES

In recent reports[1] of esophageal carcinoma it has been suggested that these tumors are far more frequent in white males, especially in those of Jewish extraction. It is the purpose of this paper to present the data from complete autopsies in 50 cases of esophageal carcinoma occurring in Negroes, Indians and mestizo persons of British West Indian and Panamanian races.

MATERIAL

The material for this study was obtained from the autopsy records of the institution with which we are associated and includes 50 histologically proved cases of carcinoma of the esophagus in the races under study. The basic data in these 50 cases are presented in tables 1 and 2.

RESULTS AND COMMENT

For statistical purposes the British West Indian and Panamanian autopsy populations can be considered here to be Negroes as shown by the finding of the sickling trait in 11 per cent of both races at autopsy.

Race, Sex and Age.—The racial distribution of esophageal carcinoma is shown in table 1. The marked preponderance of British West Indians is partially occasioned by the age group distribution of the autopsy populations,[2] more than half of the Panamanian autopsy population falling into the group in which the ages are under 41 years, in contrast to the British West Indian group. The sex and the age incidence are consistent with other reports.[1]

Incidence.—The percentage incidence for the entire 50 cases cannot be determined since some of these cases were obtained from the autopsy index system and no information is available covering the entire autopsy series in regard to the distribution by race, sex and age. However, figures are available for a fifteen and a half year period. In those statistics the British West Indian male autopsy population totaled 1,564, and of these 35, or 2.3 per cent, had esophageal carcinoma. In the female autopsy population of 591 cases there were 5 cases of esophageal carcinoma or less than 1 per cent. In the same statistics 197 British West Indian males had carcinoma, in 35, or 17.7 per cent, of whom it was in the esophagus. Similarly among the females there were 80 with carcinoma in 5, or 6.3 per cent, of whom it was in the esophagus. In the same statistics the cases of esophageal carcinoma in males were exceeded in number only by the cases of gastric carcinoma (20 per cent) and those of prostatic carcinoma (18.3 per cent).

TABLE 1.—*Data on the Distribution by Race, Sex, Age Group and Locale and the Gross Appearance of the Tumor in Fifty Cases of Esophageal Carcinoma*

	Cases
Race	
British West Indian	49
Panamanian	1
Sex	
Males	45
Females	5
Age group	
21 to 30	1
31 to 40	6
41 to 50	13
51 to 60	12
61 to 70	13
70 and over	5
Location of tumor	
Upper third	5
Middle third	25
Lower third	22
Gross appearance	
Flat	25
Polypoid	25
Ulcerated	46
Diverticular	2
Submucosal extension	14
Gross penetration	38

Etiologic Factors.—No conclusive evidence concerning the etiologic agent, or agents, pro-

1. Hollinger, P. H., and Hare, H. J.: Laryngoscope **52**:968, 1942. Vinson, P. P.: Northwest Med. **32**: 320, 1933. Mathews, R. W., and Schnabel, T. G.: J. A. M. A. **105**:1591, 1935.

2. Tomlinson, W. J., and Wilson, L. A., Jr.: Cancer Research, to be published.

ducing esophageal carcinoma was found. There were no incidental ulcers of the esophagus in the entire series. Leukoplakia was present in 2 instances, with syphilis in 1 and with no demonstrable evidence of syphilis in 1. Leukoplakia and syphilis have both been considered as possible causative factors of esophageal carcinoma. That syphilis may be a factor is strengthened by the presence of definite clinical and autopsy evidence of syphilis in 26 instances, or 52 per cent, while in 22 cases, or 44 per cent, there was no evidence of this disease at the time of autopsy, and in 2 instances a decision could not be made. The average incidence of syphilis in the autopsy population under consideration for a ten year period as determined by clinical and autopsy data was 8.7 per cent.

TABLE 2.—*Autopsy Data in Fifty Cases of Esophageal Carcinoma*

Cell type	
Squamous cell carcinoma	48
Adenocarcinoma	2
Grade of malignancy	
Grade 1	3
Grade 2	20
Grade 3	16
Grade 4	11
Direct gross extension to	
Trachea	33
Mediastinum	24
Right bronchus	17
Left bronchus	11
Aorta	10
Right pleura	10
Left pleura	8
Stomach	5
Diaphragm	4
Larynx	2
Pericardium	2
Hemorrhage from erosion of	
Esophageal veins	2
Common carotid artery	1
Metastases to	
Lungs	10
Liver	9
Ribs and vertebrae	3
Kidneys	2
Pancreas	1
Spleen	1
Peritoneum	1
Lymph nodes	
Esophageal	50
Bronchial	21
Tracheal	20
Preaortic abdominal	9
Cervical	4
Thoracic vertebral	4
Gastric	4
Thoracic aortic	2
Supraclavicular	2

In 2 cases the carcinoma was definitely recognized as having originated in a diverticulum, and it is possible that in cases of advanced or perforating carcinoma the neoplasm may have destroyed a preexisting diverticulum.

Pathologic Anatomy.—The observations at autopsy in these cases are consistent with other reports dealing with large series of cases,[1] and no detailed analysis of the material presented in tables 1 and 2 will be made beyond calling attention to the constant involvement of the periesophageal lymph nodes by the carcinoma in all cases.

SUMMARY

In British West Indian Negroes, carcinoma of the esophagus ranks third as to number of cases among all the types of carcinoma observed at autopsy.

Of the 50 persons with esophageal carcinoma, 26 had clinical and autopsy evidence of syphilis and 22 had no recognizable syphilis. A decision could not be made in regard to the remaining 2. The average incidence of syphilis in the entire autopsy population for the past ten years is 8.7 per cent.

In the 50 cases of esophageal carcinoma studied, the periesophageal lymph nodes were grossly invaded in every instance.

EXPERIMENTAL HYPERTENSION

ITS PRODUCTION IN DOGS BY INTRAVENOUS INJECTION OF STREPTOCOCCI

GEORGE F. DICK, M.D.

CHICAGO

Much has been added to present knowledge of the mechanism of hypertension by the work of Goldblatt and his associates on the renal ischemia produced by placing clamps on the renal arteries. As Goldblatt [1] put it, "Whatever may be the nature of the actual disturbance of hemodynamics which occurs in the human kidney, the seat of arterio and arteriolar sclerosis, a similar effect on hemorenal dynamics is probably produced in animals by persistent constriction of the renal artery."

With regard to the causes of such hemodynamic disturbances, Longcope and Winkenwerder [2] and Weiss and Parker [3] and others have pointed out the importance of pyelonephritis. However, there is no proof that pyelonephritis accounts for hypertension in more than a small fraction of the instances of this condition, and the actual cause of what has been called essential hypertension and of the renovascular changes associated with the late stages of the disease is unknown. Christian [3] mentioned heredity as a factor.

Some years ago G. R. Dick and I [4] called attention to hypertensive renovascular disease following scarlet fever. Earlier we [5] had observed that the urine of patients with nonsuppurative nephritis frequently contained streptococci. The urine of normal persons, on the other hand, was either sterile or contained a few organisms which are common inhabitants of the normal urethra, namely, staphylococci or diphtheroids. We also observed that after acute disturbances of focal infection, such as the extraction of a tooth, the number of streptococci in the urine increased. We [6] showed that during the severe angina in scarlet fever green-forming streptococci frequently gained entrance to the blood stream. More recently, we [7] described arterial lesions following the intravenous injection of streptococci in rabbits. I have made cultures of the urine of patients with essential hypertension and of patients with acute and chronic glomerular nephritis with hypertension and have been impressed by the frequency with which streptococci, usually Streptococcus viridans, but sometimes hemolytic streptococci, were found in the urine even when urinalysis gave no indication of renal disease.

The reports of Richards,[8] O'Kell and Elliott,[9] Hopkins,[10] Deshon,[11] Murray and Moosnick,[12a] Faillo,[13] Gudesteu Medeiros,[14] Geiger [15] and Murray and Moosnick [12b] on arterial blood cultures all indicate that bacteria gain entrance to the blood stream far more often than has been commonly supposed.

What is the result of the subjection of the body to constantly repeated invasion by bacteria in amounts insufficient to produce clinical evidence of infection?

It was to answer this question that the following work was undertaken.

EXPERIMENTAL PROCEDURE

Streptococci from various sources were injected intravenously into dogs over considerable periods. The dogs selected for these experiments were young animals which could be trained to lie quietly on a board for

From the Frank Billings Medical Clinic of the University of Chicago.

1. Lewis, H. A., and Goldblatt, H.: Bull. New York Acad. Med. **18**:459, 1942.

2. Longcope, W. T., and Winkenwerder, W. L.: Bull. Johns Hopkins Hosp. **53**:255, 1933.

3. Weiss, S., and Parker, F., Jr.: Medicine **18**:221, 1939; cited by Christian, H. A.: Osler's Principles and Practice of Medicine, ed. 15, New York, D. Appleton-Century Company, Inc., 1943, p. 937.

4. Dick, G. F., and Dick, G. R.: Scarlet Fever, Chicago, The Year Book Publishers, Inc., 1938, p. 46.

5. Dick, G. F., and Dick, G. R.: J. A. M. A. **65**: 6, 1915.

6. Dick, G. F., and Henry, G. R.: J. Infect. Dis. **15**: 176, 1914.

7. Dick, G. F., and Leiter, L.: Tr. A. Am. Physicians **54**:87, 1939.

8. Richards, J. H.: J. A. M. A. **99**:196, 1932.

9. O'Kell, C. C., and Elliott, S. D.: Lancet **2**:864, 1935.

10. Hopkins, J. A.: J. Am. Dent. A. **26**:2002, 1939.

11. Deshon, R.: Bol. Asoc. méd. de Puerto Rico **32**: 92, 1940.

12. Murray, M., and Moosnick, F.: J. Lab. & Clin. Med. (*a*) **26**:382, 1940; (*b*) **26**:801, 1941.

13. Faillo, P. S.: J. Dent. Research **21**:19, 1942.

14. Gudesteu Medeiros: Brasil-med. **56**:33, 1942.

15. Geiger, A. J.: J. Am. Dent. A. **29**:1023, 1942.

blood pressure tracings, thus making anesthesia unnecessary. The dogs were kept in cages and maintained on a diet of meat and dog chow for a time so that control mean blood pressures could be taken, urinalyses made and the blood urea and nonprotein nitrogen determined. The blood pressure was recorded by means of a kymograph and a mercury manometer connected through a large glass cannula with a gage 18 needle, which was introduced by direct puncture into the femoral artery.

A 2.5 per cent sodium citrate solution was used as the anticoagulant in the system. The blood pressure tracings were generally run ten minutes with each arterial puncture to allow the blood pressure to be stabilized. All pressures have been recorded as the means of the systolic and diastolic pressures.

After the normal blood pressure of each animal had been established, the intravenous injections of streptococci from various sources were started. These injections were given for the most part five days in the week. The amount injected depended on the condition of the animal. An attempt was always made to give doses as large as could be injected without producing obviously harmful immediate effects. Usually the injections were of twenty-four hour broth cultures of organisms, or if a good growth took longer to develop, older cultures were used.

Specimens of urine for cultures were obtained under aseptic precaution by catheterization, and, in addition to plating, cultures were made by adding 2 cc. of urine to 12 to 15 cc. of ordinary nutrient broth with a few drops of blood added.

EXPERIMENTS

Case 1.—A. W. F. was admitted to the urologic clinic of Albert Merritt Billings Hospital, April 1, 1937 with the complaint of swelling of both feet. Examination showed puffiness of the eyelids and pitting edema of both ankles. The blood pressure was 172 systolic and 94 diastolic; the urine contained albumin (1 plus), occasional cellular casts, and 7 to 8 red blood cells and 2 to 3 white blood cells per high power field; the blood urea clearance was 45; the urea content of the blood was 13.1 mg. per hundred cubic centimeters; the Wassermann test was negative.

The patient gave a history of a sinus infection, with drainage and removal of nasal polyps two weeks before entering the hospital.

Cultures of material from the nose showed many hemolytic streptococci.

Oct. 21, 1943 the patient again was seen in the urologic clinic, and the diagnosis of arteriosclerotic heart disease with hypertension was made. His blood pressure was 175 systolic and 118 diastolic. The urine showed no abnormality other than a trace of albumin.

Dog 31 (blood pressure 120; total nitrogen 9.98 Gm. per liter; plasma protein 6.06 Gm., urea 17.2 mg. and nonprotein nitrogen 28 mg. per hundred cubic centimeters).—This dog was given intravenous injections of broth cultures of hemolytic streptococci from case 1, starting April 14, 1937. The beginning dose was 50 cc. The doses were increased to 100 cc. and were injected five days a week until Oct. 4, 1941.

June 14, 1937 the dog's blood pressure had risen to 172; October 21 the pressure was 148; Feb. 16, 1938 it was 161; March 14, 1939, it had risen to 176. At the next determination, Jan. 8, 1941, the pressure was 170; March 17 it was 170; September 12, 170; October 4, 190. Jan. 13, 1942 the blood pressure was 190; February 12, 196; March 6, 190; April 9, 170.

The monthly urinalyses gave negative results until Jan. 19, 1938, when a benzidine test showed a trace of blood. January 27 the urine was normal, but February 3 it showed a trace of albumin. Thereafter it was normal at monthly examinations until Oct. 9, 1939, when there was a trace of albumin. At the monthly examinations thereafter it was normal until Aug. 27, 1940, when there was a trace of albumin; it was normal thereafter until Feb. 14, 1941, when there was again a trace of albumin. It was normal after this until April 4, 1941, when there was a trace of albumin. Some albumin was observed on several examinations after this, and on Nov. 6, 1941 the albumin was 2 plus.

Chemical examination of the blood June 10, 1937, Dec. 6, 1937, April 28, 1938 and Feb. 9, 1940 gave normal results, but May 5, 1942, seven months after the injections were discontinued, the dog became sick and chemical examination of the blood gave urea 314 mg., nonprotein nitrogen 400 mg., albumin 4.39 Gm. and globulin 4.44 Gm. per hundred cubic centimeters.

The dog died at this time with pronounced uremia. An autopsy was made four hours later.

The kidneys were contracted kidneys of the arteriosclerotic type and together weighed 31 Gm. The capsule stripped with difficulty, being adherent throughout. The cortex was narrow and light in color. The heart was large and weighed 87.9 Gm. without the contained blood. The wall of the left ventricle measured 7 to 9 mm. in thickness; that of the right ventricle, 2 to 4 mm. The aorta and the coronary arteries showed no gross change. The lungs, the liver and the spleen showed no gross change. There was some light hemorrhage throughout the gastrointestinal mucosa.

Microscopically, the alterations were most pronounced in the renal cortex. There was an increase of fibrous tissue throughout the cortex, especially surrounding the glomeruli, the tufts of which were largely replaced by hyaline material and connective tissue. Blood vessels were thickened, and there were large areas showing lymphocytic infiltration.

Summary.—Dog 31, with normal blood pressure and normally constituted blood, received intravenous injections of broth cultures of streptococci, a total of 32 liters, from April 14, 1937 to Oct. 4, 1941. Hypertension developed in three months after the first injection. Five and one-half years after the first injection and seven months after the last injection the dog died of uremia with the arteriosclerotic type of contracted kidneys.

Case 2.—F. H. S., aged 42, entered the hospital Sept. 15, 1941, complaining of disorientation, inability to talk, dyspnea on exertion and subcutaneous hemorrhages. The blood pressure was 210 systolic and 140 diastolic. The heart was 45 per cent oversize. The urine contained albumin (2 plus) and showed a hyaline cast, an occasional red blood cell, and 5 to 6 white blood cells per high power field. Str. viridans was demonstrated in the catheterized urine on culture. The Wassermann reaction was negative. The blood urea was 14.5 mg. per hundred cubic centimeters. The blood urea clearance was 41. The diagnosis was malignant hypertension with some degree of cardiac failure.

Dog 92 (blood pressure 105; weight 10.2 Kg.; urine normal).—This dog was given intravenously five times a week broth cultures of Str. viridans from the urine of case 2 from Nov. 11, 1941 to Jan. 2, 1942. This dog received a total of 2.56 liters. The urine on monthly examination remained normal. The course of the blood pressure is shown in figure 1. Fifteen months after the first injection the left kidney was removed for examination. It weighed 28 Gm. and was a trifle lighter in color than normal. The capsule stripped readily except in a few places. The surface of the kidney showed a few arteriosclerotic depressions. Micro-

scopically, there was a slight but distinct increase in connective tissue in the blood vessels and especially in the glomerular capsules.

Case 3.—D. B., aged 51, entered the hospital Sept. 3, 1942, complaining of driving pain in the back of the neck and head of three weeks' duration. This came on suddenly after he had bowled four games. The blood pressure was 230 systolic and 120 diastolic. The urine showed no abnormalities. Str. viridans was isolated from the urine on culture. The diagnosis was hypertensive vascular disease.

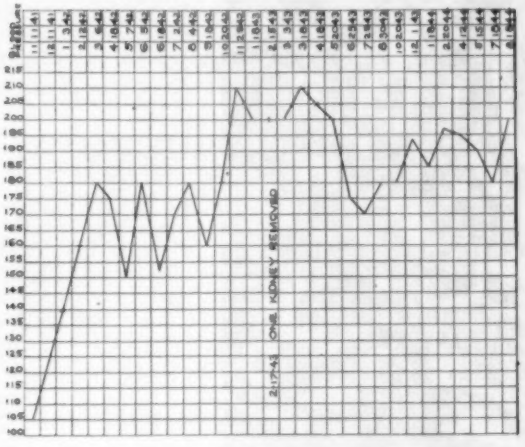


Fig. 1.—Blood pressure of dog 92 determined monthly.

Dog 147 (blood pressure 136; urine normal).—Broth cultures of Str. viridans from case 3 were injected intravenously five days a week in amounts increasing from 50 cc. to 100 cc. From Sept. 25 to Dec. 10, 1942, the dog received a total of 2.93 liters of the broth cultures intravenously. October 20 the blood pressure had risen to 146; November 29, to 166. Feb. 18, 1943 the blood pressure was 140; March 18, 174; April 9, 180. The blood urea Nov. 18, 1943, seven months after the kidney was removed, was 9.9 mg. per hundred cubic centimeters. The urine showed no abnormality on monthly examination.

April 12, 1943 the left kidney was taken out for examination. It weighed 27 Gm. and was normal except for two small areas that looked like retention cysts, about 1 mm. in diameter. Microscopically, it showed no abnormalities which could be made out on staining with hematoxylin and eosin, van Gieson or azan stains.

Dog 147 represents what might be called essential hypertension; dog 92, hypertensive vascular disease with relatively slight arteriosclerotic changes in the kidney; dog 31, death from uremia with the arteriosclerotic type of contracted kidneys. Photomicrographs of these kidneys (figs. 2, 3 and 4) show the progressing changes in the microscopic appearance of the kidneys.

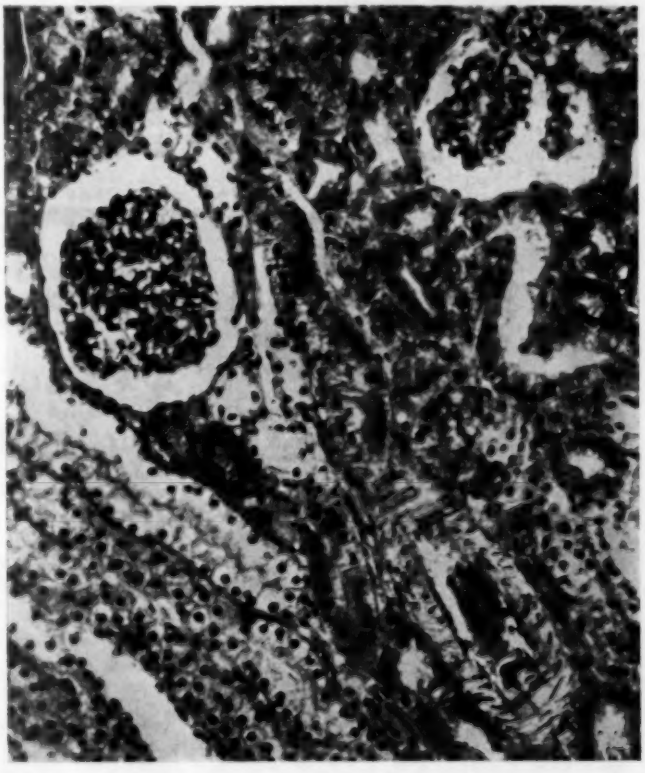


Fig. 2.—Photomicrograph of kidney of dog 147 showing no abnormality; × 250.

Case 4.—J. B., aged 38, had hypertensive cardiovascular disease. The blood pressure was 157 systolic and 118 diastolic. Urinalysis gave normal results. The blood urea was 21.2 mg. per hundred cubic centimeters. The blood urea clearance was 53.

Dog 93.—Str. viridans was isolated from the catheterized urine in case 4, and broth cultures were injected into dog 93 in amounts gradually increased to 100 cc.

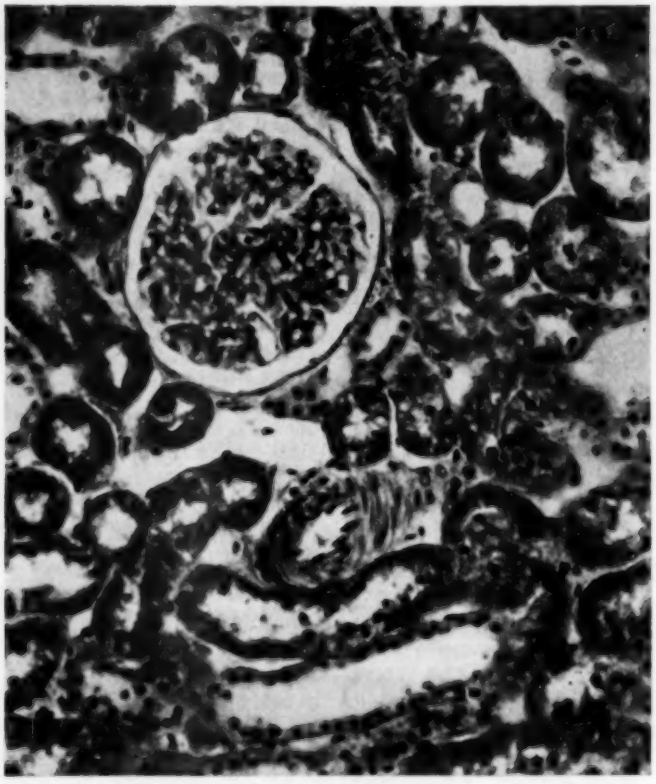


Fig. 3.—Photomicrograph of kidney of dog 92 showing slight increase in fibrous tissue; × 250.

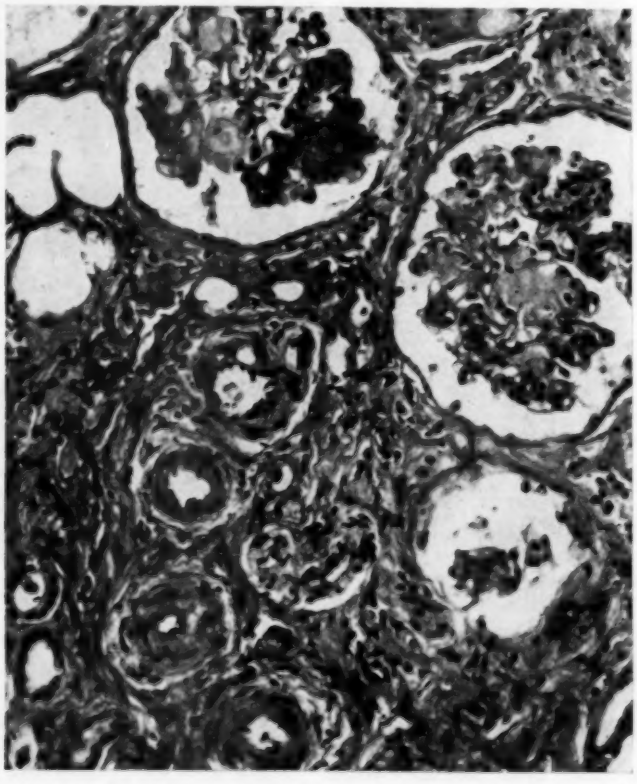


Fig. 4.—Photomicrograph of kidney of dog 31 showing the histologic picture of contracted kidney; × 250.

a day. The injections were continued as shown in figure 5. In three months the blood pressure had risen from 125 to 155 and in five months it had risen to 190.

Dog 160.—This animal received intravenous injections of cultures of the same organism, as dog 93, in approximately the same dosage. Its blood pressure remained normal for six and one-half months, when the blood pressure rose to 170.

Case 5.—E. W. M., aged 63, had hypertensive cardiovascular disease and arteriosclerotic heart disease. The

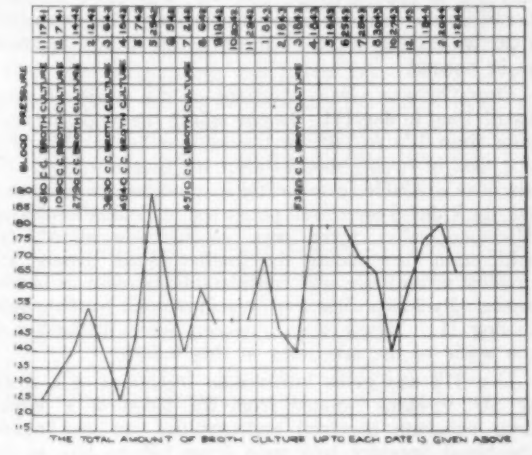


Fig. 5.—Blood pressure of dog 93, determined monthly. The total amount of broth culture injected up to each date is given above.

blood pressure was 236 systolic and 148 diastolic. The urine contained albumin (3 plus), hyaline and granular casts, an occasional red cell and 4 to 5 white blood cells per high power field. The blood urea was 11 mg. per hundred cubic centimeters. The blood urea clearance was 28. Str. viridans was isolated from the catheterized urine.

Dog 125.—Broth cultures of the organism isolated in case 5 were injected intravenously into this animal, and the blood pressure rose from 120 to 155 in one and one-half months and to 180 in five months.

Case 6.—P. R., aged 16, had acute glomerular nephritis. The blood pressure was 120 systolic and 70 diastolic. The urine contained a trace of albumin and hyaline and granular casts. Str. viridans was isolated from the catheterized urine.

Dog 36.—Broth cultures of the streptococcus from the urine in case 6 were injected in increasing amounts up to 100 cc. a day. The blood pressure of the dog rose from 105 to 154 in three and one-half months. It rose to 160 in six months, and in the seventh month the dog died of pneumonia. The kidney showed slight arteriosclerotic scarring of the surface.

Case 7.—D. H. T., aged 25, was given a diagnosis of acute nephritis and acute pansinusitis. The blood pressure was 116 systolic and 50 diastolic. The urine contained albumin (2 plus), hyaline and granular casts, many red cells, and 10 to 12 white cells per high power field. The patient had some fever, the temperature rising to 100 F. Hemolytic streptococci were present in the discharge from the nose. The blood urea was 23 mg. per hundred cubic centimeters. The urea clearance was 18. Str. viridans was isolated from the catheterized urine.

Dog 66.—This animal was started with a whole broth culture of the hemolytic streptococci from the nose and throat in case 7, given in amounts increased to 100 cc., and later this culture was lost. The injections were continued with cultures of the greening streptococci from the urine, as shown in figure 6. The blood pressure rose from 110 to 160 in twenty months. The dog died at the end of twenty-eight months. On postmortem examination there were some infarcts in both kidneys, and the cortex was thin and in part swollen with petechial hemorrhages. The capsule stripped with some difficulty, leaving an irregular surface, mottled brownish gray and yellow. The kidneys weighed together 55.5 Gm. There were some areas resembling plaques of fibrous pericarditis (soldier spots) in the pericardium, and there was some hemorrhage in the heart muscle of the left ventricle. The heart weighed 94 Gm. The liver was very light in color.

Case 8.—J. R. G., aged 2, suffered from a condition diagnosed as acute nephritis following tonsillitis. The blood pressure was 130 systolic and 77 diastolic. Str. viridans was isolated from the catheterized urine. The organism produced considerable hemolysis in contrast to other organisms described.

Dog 158.—The dog was given intravenous injections of the streptococci isolated in case 8. After receiving only 60 cc. in three injections the blood pressure rose from 130 to 170 in nine days.

Case 9.—B. B., aged 63, was given a diagnosis of hypertensive cardiovascular disease with aortic stenosis. The blood pressure was 220 systolic and 130 diastolic. The blood urea was 9.4 mg. per hundred cubic centimeters. The urea clearance was 62. The urinalysis gave negative results. Str. viridans was isolated from catheterized urine and, like the streptococcus isolated in case 8, produced a wide zone of hemolysis as well as greening.

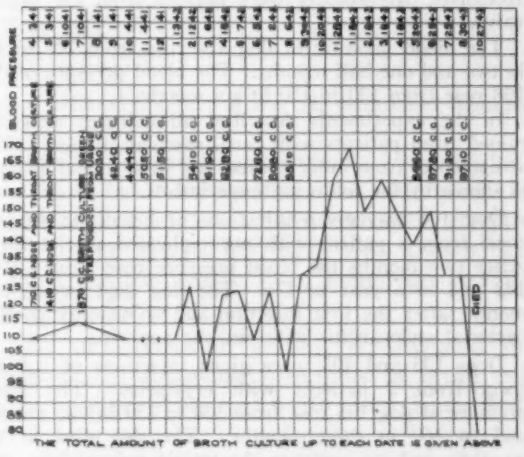


Fig. 6.—Blood pressure of dog 66 determined monthly. The total amount of broth culture injected up to each date is given above.

Dog 155.—This dog, weighing 6.2 Kg., received intravenous injections of a broth culture of the streptococcus from the urine in case 9. The blood pressure rose from 135 to 150 one year afterward, and the dog died ten days later, three months after the last injection. The kidneys weighed 42 Gm. together. They were lighter in color than normal, and they had many arteriosclerotic depressions on the surface, but the capsule

stripped readily. The cortex was not perceptibly narrowed. Hemolyzing, green-forming streptococci were grown from the kidney in pure culture.

Microscopically, there was not much change but there were areas of extensive plasma cell infiltration, some thickening of the arterioles and congestion of the glomeruli, with some red cells in Bowman's capsule. The cause of death in the animal was not clear. It was a pup about 4 months old when the injections were started.

Case 10.—R. S., aged 57, had a diagnosis of coronary arteriosclerosis. The blood pressure was 148 systolic and 94 diastolic. The urinalysis gave negative results. A hemolytic streptococcus was isolated from the throat.

Dog 101.—A broth culture of the hemolytic streptococcus isolated from the throat in case 10 was injected into this dog. In two months the blood pressure rose from 120 to 150, and two years later it was 160; three years later it was 185.

Summary of Further Experiments.—Dogs 109, 1, 174 and 168 were all given injections of cultures of hemolytic streptococci from the throats of patients with glomerular nephritis. Further details will not be given in order to save space. The blood pressure of dog 109 rose from 120 to 165 in one month and to 185 in one year. Injections were given at intervals from Jan. 5, 1942 to July 20, 1944. Dog 1 received injections from Feb. 11, 1935 to Feb. 1, 1939 and again from Aug. 26, 1940 to Feb. 8, 1941, when he died. The blood pressure remained normal for four years and then rose to 150; eight months later it was 170. At postmortem examination the dog was found to have endocarditis with vegetation along the entire mitral valve and hemorrhages in the myocardium. The kidneys showed embolic nephritis superimposed on an arteriosclerotic condition. There were hemorrhages in the mucosa of the gastrointestinal tract. The thoracic and abdominal portions of the aorta were normal. Hemolytic streptococci were isolated from the cardiac valve.

The blood pressure of dog 174 rose from 120 to 165 in two and one-half months. The blood pressure of dog 168 rose from 130 to 150 in six months.

In the experiments described all cultures were obtained from patients with renal-vascular disease. That streptococci from other sources act in a similar manner is shown by the following experiments.

Dog 104 was given injections of hemolytic streptococci from a patient with uncomplicated scarlet fever. After two months the blood pressure rose from 110 to 142 and in a year to 176. The dog died twenty-two months after the first injection and on autopsy showed bacterial endocarditis with embolic nephritis.

Dogs 135 and 105 were given injections of streptococci from 2 patients with erysipelas. The blood pressure of dog 105 rose from 130 to 150 in two months and to 160 in three months. The dog died in ten months, and at autopsy bacterial endocarditis was observed along with hemorrhagic pericarditis. The blood pressure of dog 135 rose from 120 to 140 in two months and to 155 in six months. The animal died eleven months after the first injection. The autopsy showed early bacterial endocarditis with embolic nephritis.

On account of the frequency with which hypertension follows chronic pyelonephritis, dogs 111 and 120 were given injections of colon bacilli. The blood pressure of dog 111 rose from 120 to 160 in one month and reached 184 in eleven months. The dog died seventeen months after the first injection. The autopsy showed hemorrhages in the peritoneal coat of the colon. The kidneys weighed 50 Gm. together. The capsule could not be stripped without pulling with it part of the cortex and leaving an irregular surface. The heart weighed 70 Gm. and except for a pale myocardium showed no other change. The aorta was normal. Microscopically, the kidneys showed an increase in the fibrous tissue with some hyaline change. Many of the glomeruli were shrunken and contained what was probably albuminous material within Bowman's capsule. Pyelitis was present, and a large amount of infiltration with round cells. Many of the tubules were dilated and contained either hyaline or granular casts. The increase in fibrous tissue, however, was more apparent between the tubules and surrounding the glomeruli than within the walls of the arteries, which appeared to be normal.

Dog 120 was given injections of the strain of colon bacilli used in dog 111. In one month the blood pressure rose from 120 to 140; in twelve months, to 150. The dog died in twenty months after the first injection. No one was available to make the postmortem examination, but the kidneys were well preserved in Zenker's solution. Microscopically, there was considerable round cell infiltration surrounding the smaller blood vessels, and in some areas there was considerable increase in fibrous tissue. Pyelonephritis was present, similar to that found in dog 111. There was, however, some thickening of the walls of the arterioles in this kidney.

Dog 113 was given intravenous injections of a strain of Str. viridans isolated from the blood of a patient with subacute bacterial endocarditis. In one month the blood pressure had risen from 135 to 160, in ten months to 190, in two years to 196. Although injections were stopped after six months, the lowest monthly blood pressure obtained was 170.

Dogs 64 and 96 were both given intravenously a culture of staphylococci from a postoperative suppuration. The blood pressure of dog 64 rose from 100 to 145 in eight months and in nine months to 155. The dog died in fifteen months, one day after the last injection, after receiving a total of 8,340 cc. of broth cultures of staphylococci. The autopsy showed petechial hemorrhages throughout the bowel and in the endocardium. Duodenal ulcers were present. The kidneys were somewhat light in color; the capsule stripped with some difficulty, and some of the cortical tissue was removed with it.

The blood pressure of dog 96 rose in one month from 130 to 160, in ten months to 165, in thirteen months to 180. From that time the monthly variations were large, with the pressure as low as 130 in one instance and 150 in several instances; in three years it was 180. This dog is still alive. The total amount injected was 5,430 cc.

It is apparent, then, that the intravenous injections of streptococci in dogs is followed by a rise in their blood pressure and that this happens whether the streptococci are isolated from patients with hypertension or from patients without hypertension or are from stock cultures. It happens with green-forming streptococci, with hemolytic streptococci, and with streptococci producing both greening and hemolysis on blood agar plates. How many other varieties of bacteria may produce hypertension in dogs we do not know. Forsbeck[16] stated that hypertension

16. Forsbeck, F. C.: Science **80**:478, 1934.

is more likely to occur in typhoid carriers than others of the same age. Injections of colon bacilli were followed by hypertension as described. However, the lesions in the kidney were somewhat different from those produced by streptococci, especially in that pyelonephritis was present. With injections of staphylococci, also, hypertension was produced. With organisms other than Str. viridans, the pathologic picture produced is likely to be more complicated, and failure to produce hypertension is more common, owing to the fact that the animal dies shortly after the beginning of injections either from toxic effects or septicemia and pyemia with or without endocarditis. In general it seems easier to produce uncomplicated hypertension with less virulent organisms, since it is difficult to regulate the dose of the more virulent organisms so as to avoid fatal disease before or after hypertension has time to develop. Most commonly these fatalities were observed with organisms from subacute bacterial endocarditis.

It is of interest to note that in 9 dogs with hypertension the average weight of the heart was 8.51 Gm. per kilogram of body weight, whereas the average weight of the heart in normal dogs was 7.25 Gm. per kilogram.

That hypertension does not invariably follow intravenous injections of streptococci, even when the organisms are given in doses which do not cause these complications, is shown in dog 91. This dog was given injections of the same culture and at the same time as dog 92. While the blood pressure rose in dog 91 to 140, it never went higher, and at the end of three years and four months the dog died. At autopsy the kidneys weighed 67 Gm. They showed increased consistency and were lighter in color than normal. The capsule when stripped left a distinctly granular surface, with the nodules making up the surface varying in size to that of a rice grain. The heart weighed 81 Gm. Microscopically, the changes in the kidneys were similar to those described in the biopsy specimen of the kidney of dog 92. Figures 2 and 7 show the difference of the variations in blood pressure of these two animals.

In 8 other instances dogs received the same injections of streptococci as did others in which hypertension developed, and in the case of both green-forming and hemolytic streptococci no hypertension followed, although slight arteriosclerotic changes in the kidney were observed in 4. It is possible that in some of these dogs hypertension would have developed later.

The failure to produce hypertension in such instances gives rise to the question whether the increases in the instances in which the blood pressure did rise after injections of streptococci were coincidences and represented spontaneous increases which would have occurred in the dogs whether bacterial injections were made or not. The question is the more pertinent because the percentage of dogs found with spontaneous hypertension is considerable. However, of the total number of dogs given injections in which immediate death, endocarditis, septicemia or other reasons prevented any chance of hypertension following, 31, or 73.4 per cent, presented hypertension, and 11, or 26.2 per cent, did not. Moreover, in selecting dogs for this work, of 99 dogs examined, only 20, or 20.2 per cent, had to be discarded on account of hypertension.

On account of this fact, it seems reasonably certain that the injections caused the following hypertension. It is not unlikely that the hypertension that occurred spontaneously in our dogs may have been due to infections. Many of the animals were found to have hemolytic streptococci in the throat, and it is well known that dogs frequently suffer from hemolytic streptococcic tonsillitis.

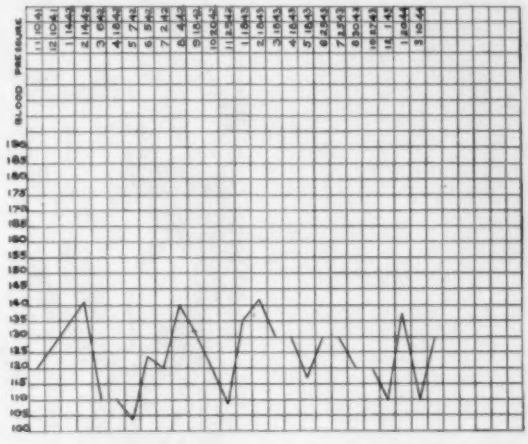


Fig. 7.—Blood pressure of dog 91, determined monthly.

The next question arising is: Would the hypertension following injections of broth cultures have occurred had broth alone been used?

As long ago as 1913 Longcope[17] described renal lesions following injections of horse serum and egg albumin in dogs and rabbits. These lesions showed round cell infiltration, degeneration and connective tissue proliferation.

Dogs 161, 167 and 173 were given injections of sterile broth identical with that used in making the broth cultures employed in the preceding experiments; the same technic was used, but the broth was injected in larger quantities. Dog 161

17. Longcope, W. T.: J. Exper. Med. **18**:678, 1913.

received 7,000 cc. of broth intravenously over a period of thirteen months. The initial blood pressure was 130. The blood pressure rose in five months to 160 but in eight months more was only 145.

Dog 167 received 6,190 cc. of broth intravenously in ten months. At the time the injections were started the blood pressure was 140. It did not rise above this point, and ten months later was 135.

Dog 173 received 7,380 cc. of broth over a period of ten months. The blood pressure rose from 125 to 155 in this time.

It will be seen that while some rise in blood pressure occurred following intravenous injections of broth, it was not great in degree, although large quantities of broth were used over a period in which much higher pressures were produced with smaller amounts of bacterial cultures.

CONCLUSION

Hypertensive states comparable to essential hypertension and hypertensive renovascular disease in man have been produced in dogs by intravenous injections of streptococci and other bacteria.

OSSIFIED CARTILAGE WITH MYELOID FAT MARROW IN THE AORTIC RING OF A RABBIT

W. C. HUEPER, M.D.
NEW YORK

Vanzetti [1] and Hueper [2] have recorded the relatively frequent occurrence of hyaline cartilaginous plates of the aortic ring in rabbits. They considered these formations as the result of normoplastic metaplasia of fibrous tissue. Dratschinski [3] made similar observations but regarded the formations as pathologic reactions.

The presence of cartilaginous plates in the aortic ring has been reported in other species, such as mice, rats, sheep, buffaloes, horses, turtles, alligators and chickens (Hueper [2]). Enchondral ossification of these foci was seen in sheep of advanced age. Hueper [4] recently recorded the occurrence of bone with myeloid marrow in a cartilaginous focus at the base of the aorta of a dog.

The present report deals with a similar lesion in the aortic ring of a rabbit which had received in its daily diet 0.25 Gm. of cholesterol in oil and 10 cc. of a 1 per cent aqueous solution of the detergent Triton K-60.[4a] The aorta of this animal showed in the intima numerous cushions of foam cells and in the aortic ring a large focus of cancellous bone surrounded by traces of cartilaginous tissue. The marrow cavities of the bone were filled with fat tissue containing a

A focus of cancellous bone surrounded by traces of cartilaginous tissue in the aortic ring of a rabbit. In the bone note marrow cavities filled with fat tissue and a scattering of immature myeloid cells.

From the Warner Institute for Therapeutic Research.

1. Vanzetti, F.: Arch. ital. de biol. **56**:265, 1911.
2. Hueper, W. C.: Arch. Path. **27**:466, 1939.
3. Dratschinski, cited by Gruber.[7]
4. Hueper, W. C.: J. Am. Vet. M. A. **101**:493, 1942.

4a. Triton K-60 is cetyldimethyl benzylammonium chloride (Röhm & Haas Co., Inc.).

moderate scattering of immature myeloid cells (figure).

This observation is of interest not only because of its rarity but also because cartilaginous and osseous tissue with myeloid marrow occurs in the walls of sclerotic aortas and arteries of rabbits and man. Harvey [5] recorded the presence of osseous tissue with marrow in the abdominal aorta of the rabbit following the painting of the outside of the vessel with a 3 per cent solution of silver nitrate or a 2 per cent solution of copper sulfate. Seegal and Seegal [6] noted the spontaneous formation of bone and marrow in the aorta of a rabbit. The incidence of myeloid tissue in aortic lesions of this type seems to be low, as cartilaginous foci in the aortic media are not infrequent in spontaneous arteriosclerosis in rabbits [7] and have been observed in the medial aortic lesions of rabbits induced by the injection of epinephrine hydrochloride.[8]

While ossification of calcified foci in the intima and the media of the sclerotic aorta and of the femoral, carotid and uterine arteries in man is not unusual,[9] the presence of myeloid tissue in such lesions is apparently infrequent.[10] Freudenstein [10d] asserted that the appearance of hematopoietic tissue in the calcified vascular wall depends on the development of vascular structures invading the calcified matter. The myeloid tissue derived from these vessels precedes the ossification. Cartilaginous tissue either alone or in connection with osseous tissue is rarely encountered in the walls of human arteries and in those animals other than rabbits.[11]

SUMMARY

Metaplastic transformation of a cartilaginous plate in the aortic ring of a rabbit into cancellous bone with myeloid tissue was observed.

5. Harvey, W. H.: J. M. Research **17**:1, 1907.

6. Seegal, B. C., and Seegal, D.: Arch. Path. **3**:73, 1927.

7. Gruber, G. B.: Virchows Arch. f. path. Anat. **275**:541, 1930.

8. Miesowicz, E.: Centralbl. f. allg. Path. u. path. Anat. **18**:8, 1907. Erb, W.: Arch. f. exper. Path. u. Pharmakol. **53**:173, 1905. Trachtenberg, M. A.: Centralbl. f. allg. Path. u. path. Anat. **17**:611, 1906. Otto, C.: Virchows Arch. f. path. Anat. **203**:352, 1911. Studzinski, cited by Gruber.[7]

9. Mönckeberg, I. G.: Virchows Arch. f. path. Anat. **167**:191, 1902. Sappington, S. W., and Fisher, H. R.: Arch. Path. **34**:989, 1942. Cohn, cited by Gruber.[7] Huebschmann, P.: Beitr. z. path. Anat. u. z. allg. Path. **39**:119, 1906. Weizmann, M.: Systematische histologische Untersuchungen über den Ductus resp. das Ligamentum Botalli im Anschluss an einen Fall von Verknorpelung des letzteren, Inaug. Dissert., Zurich, A. Schereschewsky, 1911. Jores, L.: Arterien, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 639. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, ed. 7 and 8, Berlin, Walter de Gruyter & Co., 1922, vol. 1, p. 78. Wolkoff, cited by Nieberle, K.: Verhandl. d. deutsch. path. Gesellsch. **25**:291, 1930. Rohmer, P.: Virchows Arch. f. path. Anat. **166**:13, 1901. Ceelen, cited by Röpke: Klin. Wchnschr. **11**: 921, 1932. Bunting, C. H.: Folia haemat. **3**:244, 1906; J. Exper. Med. **8**:365, 1906. Bürger, L., and Oppenheimer, A.: J. Exper. Med. **10**:354, 1908. Howse, H. G.: Tr. Path. Soc. London **28**:90, 1877. Marchand, M., in Eulenburg, A.: Real-Encyclopedie der gesamten Heilkunde, ed. 3, Leipzig, Urban & Schwarzenberg, 1894, vol. 2, p. 203. Orth, J.; Lehrbuch der speciellen pathologischen Anatomie, Berlin, A. Hirschwald, 1883, vol. 4, p. 225. Bensen, G.: Beiträge zur Kenntnis von der heteroplastischen Knochenbildung, Inaug. Dissert., Göttingen, 1898. O'Brien, L. J.: Ueber Verknocherungsvorgänge in den Arterien, Inaug. Dissert., Würzburg, C. J. Becker, 1902. Poscharissky, cited by Gruber.[7]

10. (*a*) Borchardt, H.: Virchows Arch. f. path. Anat. **259**:373, 1926. (*b*) Edelmann, A.: ibid. **266**: 51, 1927. (*c*) Thiersch, H.: Beitr. z. path. Anat. u. z. allg. Path. **96**:147, 1935-1936. (*d*) Freudenstein, M.: Frankfurt. Ztschr. f. Path. **2**:591, 1909. (*e*) Rosenstein, P.: Virchows Arch. f. path. Anat. **162**:100, 1900.

11. Marburg, O.: Centralbl. f. allg. Path. u. path. Anat. **13**:300, 1902. Lillie, R. D.: Arch. Path. **18**: 710, 1934. Spiegl, A.: Virchows Arch. f. path. Anat. **231**:224, 1911.

EFFECTS OF AN ABORTIFACIENT PASTE ("UTRA-JEL")

REPORT OF A DEATH FROM ITS USE AND OF AN EXPERIMENTAL STUDY OF ITS EFFECTS ON RABBITS AND RATS

R. STRAUS, M.D., AND N. DE NOSAQUO, M.D.
LOS ANGELES WASHINGTON, D. C.

The use of abortifacient pastes to produce abortion, as contrasted with other methods, is relatively uncommon. Except for an occasional editorial comment [1] and isolated reports,[2] information concerning the morbidity and the mortality resulting from the use of such pastes has not received much attention in the American and British medical literature. In the German literature extensive reports have appeared, concerned chiefly with deaths from peritonitis, intravascular hemolysis and air and fat embolism following the use of such pastes as "Interruptin," Leunbach's paste, "Interferin" and "Provokol." [3]

REPORT OF A CASE

E. M., a 22 year old white woman, about six weeks pregnant, was made to abort by a physician who introduced an abortifacient paste into the uterus twice at a two day interval. That an abortifacient paste was used, however, was not known until after the official investigation. The patient began to bleed from the vagina twenty-four hours after the second injection. The following day nausea, vomiting and generalized abdominal pain developed, which ultimately localized in the right lower quadrant of the abdomen.

She was admitted to a hospital on the fifth day of illness. The body temperature was 100.4 F. She appeared toxic and presented signs of peritonitis in the lower portion of the abdomen. She was treated with repeated blood transfusions and sulfathiazole for the infection, with morphine for the pain and with general supportive measures. Later pyuria developed, followed by urinary retention. Abdominal distention was also present. A mass gradually developed in the left lower quadrant of the abdomen. This suddenly decreased in size when an abscess ruptured spontaneously into the rectum on the forty-second day in the hospital. On the forty-fifth day in the hospital laparotomy revealed that the entire pelvis was filled with a hemorrhagic and purulent exudate. Her course in the hospital was downhill and was characterized by a high spiking temperature. Death occurred on the fifty-sixth day in the hospital.

Autopsy.—Because of the homicidal aspects of the case, the body was brought to the coroner's office of Cuyahoga County in Ohio, where the autopsy was made by one of us (R. S.). The body was moderately emaciated. The incision in the abdomen was partially healed in the upper half and infected in the lower half. The labia were edematous. The gastrointestinal tract was distended, and loops of small intestine in the lower half of the abdomen were adherent. Between the loops were pockets of purulent and hemorrhagic exudate. Approximately 500 cc. of firm blood clot and purulent exudate filled the pelvis. A perforation, 2 cm. in diameter, passed from the cul-de-sac into the rectum.

The organs revealed no significant abnormality apart from the genitourinary system. The ureters were slightly constricted at their lower ends, owing to the local inflammation; they and the renal pelves were moderately dilated and hyperemic. The kidneys were slightly enlarged and showed severe ascending pyelonephritis.

The uterus was small but soft. The inner surface was greenish gray and irregular. The myometrium was similarly discolored and edematous. Near the right cornu of the fundus was a perforation 8 by 4 mm. in diameter. The edges of the defect were rounded and greenish gray. The cervix was elongated; the external os showed healing lacerations, the tissues being discolored and edematous. Microscopically, the endometrium was extremely thin, regenerative in type, with moderate inflammation and areas of metaplasia to stratified squamous epithelium. Considerable hemosiderin was present, chiefly within endothelial phagocytes. The myometrium was edematous and moderately infiltrated with leukocytes. The sections from the area

This study was supported by the Zeiler Memorial Research Fund, aided in part by grants from Mr. J. Copeland and Mr. B. Oberstein.

From the Laboratories of the Cedars of Lebanon Hospital, Los Angeles (Dr. Straus), and the Food and Drug Administration, Federal Security Agency, Washington, D. C. (Dr. De Nosaquo).

Dr. G. A. Granger made the original investigations in this field for the Federal Security Agency in connection with the enforcement of the Federal Food, Drug and Cosmetic Act.

1. Abortifacient Pastes, report of Bureau of Investigation, J. A. M. A. **98**:2155, 1932; Interferin, Queries and Minor Notes, ibid. **105**:1210, 1935; Abortion and Leunbach's Paste, editorial, ibid. **111**:535, 1938; Abortifacient Pastes, editorial, ibid. **115**:221, 1940; Abortionists Sentenced, Medical News (Minnesota), ibid. **115**: 227, 1940.

2. Ridell, G. A.: J. Obst. & Gynaec. Brit. Emp. **39**:1, 1932. D'Amour, F. E., and Kiven, N.: Am. J. Obst. & Gynec. **29**:503, 1935. Weilerstein, R. W.: J. A. M. A. **125**:205, 1944.

3. Wolfe, H.: Monatschr. f. Geburtsh. u. Gynäk. **88**:442, 1931. Pankow and Pfleiderer: Zentralbl. f. Gynäk. **56**:865, 1932. Sellheim, Weischsel, Kustner, Schweitzer and Vogt: ibid. **56**:750, 1932. Engelmann, F.: Deutsche med. Wchnschr. **58**:166, 1932. Wagner, G. A.: Monatschr. f. Geburtsh. u. Gynäk. **90**:445, 1932. Engelmann, F.: Zentralbl. f. Gynäk. **56**:119, 1932. Sellheim, H.: Monatschr. f. Geburtsh. u. Gynäk. **90**:441, 1932. Leunbach, J. H.: ibid. **90**:446, 1932. Otto, K.: Zentralbl. f. Gynäk. **56**:112, 1932. Brach, E.: ibid. **56**:122, 1932.

of perforation revealed most extensive inflammation. In addition, embedded deep in the myometrium were irregular masses of orange-colored, somewhat granular material with a vacuolated and hyalinized background, resembling agglutinated masses of blood clot as though altered in part by chemical agents (fig. 1). A few multinucleated foreign body giant cells were present near this material. The myometrium around it was diffusely necrotic, with only phantoms of the former structures. Organizing blood clot and purulent exudate in which were embedded small masses of the material just described covered the perimetrium.

The ovaries and tubes were buried in a mass of exudate. In one ovary were a number of infected follicular cysts and abscesses in some of which could be seen a few small masses of vacuolated, deeply orange-stained material like that described in the uterus, with a similar foreign body giant cell reaction.

Smears and cultures of the peritoneal exudate gave a mixed flora with Bacillus coli predominating in the cultures. The postmortem blood culture from the heart produced a luxuriant growth of Bacillus welchi.

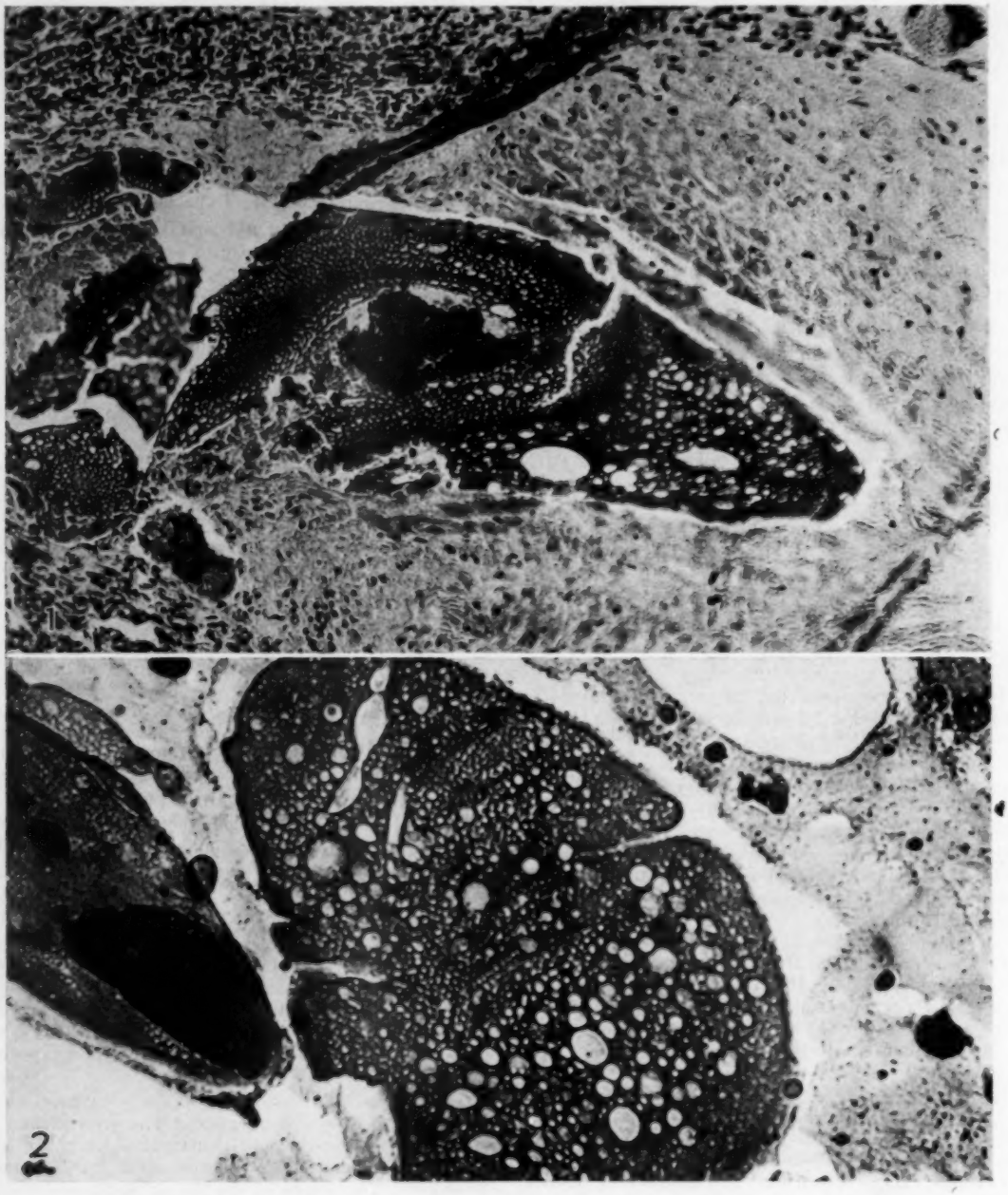


Fig. 1.—Lesion in a human uterus treated by injection of an abortifacient paste.
Fig. 2.—Effect of the paste on human blood in vitro.

Because of the perforation in the uterus, the abortion at first was believed to be due to mechanical procedures, though a caustic chemical was suspected when on microscopic examination the orange-stained material with the regional foreign body reaction was seen. Official investigation revealed that an abortifacient paste had been used, and trial of the physician who injected the paste resulted in his conviction for manslaughter.

The results of a chemical analysis of the paste ("utrajel") were reported as follows:

Castor oil–potassium hydroxide soap	35.1 to 47.3	per cent
Pine oil	10.3 to 25.2	per cent
Alkali-combined iodine	1.1 to 1.6	per cent
Water	34.9 to 44.5	per cent
p_H	8.1 to 9.49	

Since little is known of the effects of this paste, we decided to investigate its effects on human blood in vitro and in pregnant animals.

ACUTE EXPERIMENTS WITH ABORTIFACIENT PASTE

Effect on Human Blood in Vitro.—The abortifacient paste (0.5 cc.) was added to fresh human blood (5 cc.) in a test tube. This mixture was shaken vigorously for two minutes, allowed to stand for thirty minutes, then fixed with about five volumes of a neutral 4 per cent solution of formaldehyde for twenty-four hours. The solid portions of this mixture were then dehydrated in the usual procedure, embedded in paraffin, sectioned at 10 microns and stained with hematoxylin and eosin.

Almost immediately after the paste was added to the blood and shaken, the blood turned dark brown and became lumpy. The microscopic preparations of this material revealed a striking alteration of the blood clot (fig. 2). The erythrocytes were no longer recognizable. Instead there were irregular masses of coarsely vacuolated material which was in part granular and in part hyaline. This tissue was deeply orange stained and presented a distinct similarity to the vacuolated masses found in the uterus and the ovary of the patient.

Effect on Uterus of a Pregnant Rabbit.—One healthy female rabbit, weighing approximately 6 pounds (2.7 Kg.), well along in pregnancy, was used. With the animal under anesthesia, approximately 0.5 cc. of the abortifacient paste was injected in three places in the left horn of the uterus. One morning, a week later, the rabbit was found dead.

There was perforation of the uterus at one of the sites of injection. Generalized purulent peritonitis was present. No fetuses were found in either horn of the uterus. Portions of the tissues were fixed in a neutral 4 per cent solution of formaldehyde, dehydrated, sectioned and stained in the usual manner. Histologic examination revealed an extensive necrotizing inflammation of the left uterine horn at the sites of injection. In the wall at the site of perforation and in the lumen could be seen numerous small masses of vacuolated granular and hyaline material similar to those described in the human uterus and ovary. This material was not seen in the opposite horn of the uterus nor in sections of the heart, the lungs, the liver, the spleen and the kidney.

Effect on the Uterus in Pregnant White Rats.—In 2 healthy pregnant white rats, each weighing about 200 Gm., approximately 0.5 cc. of the abortifacient paste was injected into the vagina, and a cotton plug was inserted to prevent its escape. In 2 other pregnant rats, under anesthesia induced with ether, approximately 0.1 cc. of the abortifacient paste was injected into the wall and the lumen of the right horn of the uterus in five places, each the site of a rat embryo. The left horn of the uterus was reserved as a control. Seven days later all the animals were killed, and the tissues were sectioned in the usual manner.

Histologic examination of the uterus revealed in each instance an extensive suppurative inflammation of the inner surface. In 1 rat an inflammatory stricture prevented the expulsion of two fetuses. All the others had been aborted. In the lumen between the dead fetuses and the uterine wall could be seen small, irregular, vacuolated granular and hyaline masses of material, similar to those seen in the human uterus and ovary (fig. 3). Both the uterine wall and the tissues of the embryos around these masses showed gangrenous necrosis as though acted on by a diffusible toxic agent. Sections of the heart, the lungs, the liver and the kidneys revealed no significant abnormality.

No alterations were noted in the tissues, including the vagina and the uterus, of those rats treated intravaginally with the paste.

CHRONIC EXPERIMENTS WITH THE ABORTIFACIENT PASTE

Five healthy pregnant white rats, each weighing about 200 Gm., were anesthetized, and approximately 0.1 cc. of the paste was injected into the right horn of the pregnant uterus of each animal in from two to seven places. One animal died five days later. The remaining animals were killed forty-three days later. Tissues from all were sectioned and prepared in the usual manner.

Examination of the animal that died five days after being given injections revealed extensive generalized acute peritonitis secondary to a perforation of the uterus. The fetuses had been aborted. Histologic examination of the tissues showed extensive inflammation and characteristic vacuolated granular and hyaline masses similar to those in the acute experiment.

Examination of 2 of the remaining rats on the forty-third day after injection revealed no evidence of the fetuses. These animals showed no gross or histologic abnormality except for a diffuse eosinophil infiltration in the wall of the treated horn of the uterus. It is suspected that the paste was injected wholly into the lumen of the uterus in these animals and was then expelled. In the other 2 animals, inflammatory strictures caused the retention of two fetuses in one animal and only one fetus in the other. The fetuses were autolyzed. There was extensive chronic inflammation of the uterine wall with considerable regional fibrosis, chiefly in the region of the injection. Here, too, were numerous irregular masses of vacuolated granular and hyaline material, with regional foreign body giant cells and xanthoma cells (fig. 4). This closely resembled the lesion in the human uterus and ovary.

EXPERIMENTS WITH THE COMPONENTS OF THE ABORTIFACIENT PASTE

Ingredients Added to Human Blood in Vitro.—Approximately 0.5 cc. amounts of castor oil, castor oil soap prepared with sodium hydroxide, oil of pine needles, 5 per cent sodium hydroxide and decolorized tincture of iodides were added, respectively, to 2 cc. amounts of human blood in test tubes. The mixtures were shaken vigorously for about two minutes and allowed to stand for thirty minutes; then the solid portions were fixed, sectioned and stained in the usual manner.

Sodium hydroxide, castor oil and castor oil soap when added to the blood produced a brown discoloration immediately after being mixed, while the oil of pine needles and the tincture of iodides caused a delayed and less pronounced discoloration. Sections of the solid portions of these mixtures revealed a complete loss of cellular elements of the blood and only small irregular amorphous and granular masses of orange and brown material remaining in places. Nowhere did these resemble the lesion seen in figure 2.

Ingredients Injected into the Uterus of White Rats.—In 5 nonpregnant healthy white rats, each weighing

about 200 Gm., in several places in one horn of the uterus was injected approximately 0.2 cc. of castor oil, castor oil soap, oil of pine needles, decolorized tincture of iodides and 5 per cent sodium hydroxide, respectively. The animal given the injection of oil of pine needles died within thirty minutes. The animal given the injection of 5 per cent sodium hydroxide died on the second postoperative day. The other 3 rats were killed on the thirty-fourth day. The tissues of all the animals were prepared, sectioned and stained in the usual manner.

The animal given the injection of oil of pine needles revealed no characteristic changes either grossly or microscopically. Death was probably due to the toxic effect of this oil. Postmortem examination of the animal receiving sodium hydroxide revealed extensive local necrosis and inflammation but no characteristic lesion. The remaining animals, given injections of decolorized tincture of iodides, castor oil and castor oil soap, respectively, revealed only varying degrees of suppurative inflammation and focal necrosis.

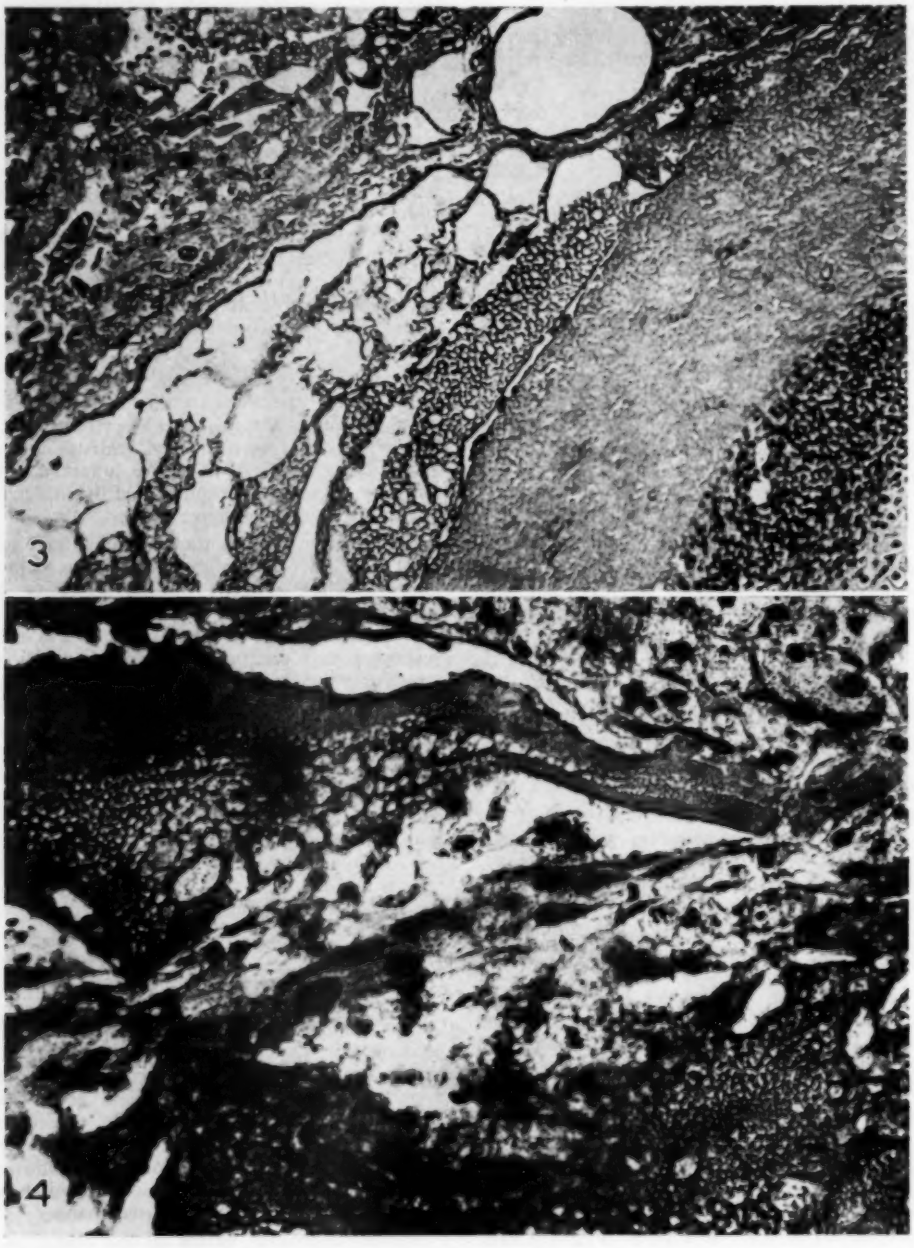


Fig. 3.—Effect of the paste on the uterus of a pregnant white rat. Note a portion of a retained fetus on the right (seven days).

Fig. 4.—Effect of the paste on the uterus of a pregnant white rat (forty-three days).

COMMENT

The death of the patient was undoubtedly due primarily to the use of the abortifacient paste. Apparently the paste was sufficiently caustic to perforate the pregnant uterus and even erode

one ovary. The necrotizing action of the paste was demonstrated by the gangrenous necrosis of the uterine and fetal tissues in the rabbits and the rats, and the erosive action was apparent from the perforation of the uterus in 2 of the animals.

Characteristic of the effects of this paste are irregular, vacuolated, partially hyaline and partially granular masses, which are different from the lesions seen in other types of abortion or poisoning. As demonstrated by the in vitro experiments, characteristic masses are produced by the action of the paste on blood. The erythrocytes are laked and the proteins of the cells and the serum agglutinated into the granular and hyaline masses. The orange discoloration of these masses is due chiefly to the oil of pine needles and to some extent to the alkali. The vacuoles appear to be produced by enmeshed droplets of castor oil and oil of pine needles.

Once formed, these masses may remain in situ and induce granulomatous inflammation with foreign body giant cells. This result was well shown by the lesions in the human uterus and in the chronic experiments on white rats.

Since it was impossible to reproduce the lesion with any of the component parts of the paste, either in vitro or in animals, this lesion is believed to be characteristic of the paste as a whole.

SUMMARY

A 22 year old white woman was caused to abort by intrauterine injections of an abortifacient paste. The paste appears to have been caustic and to have produced perforation of the uterus with generalized peritonitis and death. Masses of material believed to be the result of the action of the paste on blood were observed microscopically in the uterus, in the perimetrial exudate and in the ovary. Human blood mixed with the paste in vitro produced masses of material with microscopic characteristics similar to those in the human uterus. In a pregnant rabbit and in white rats the paste when injected into the uterus produced changes similar to those observed in the human uterus. The component parts of the paste when mixed one by one with human blood or when injected singly into the uterine wall in white rats failed to reproduce masses similar to those described.

The masses of material herein described are unlike any associated with other types of abortion and are probably characteristic of the type of abortifacient paste used.

ADENOMYOEPITHELIOMA (CYLINDROMA) OF PALATAL MUCOUS GLANDS

WILLIAM H. BAUER, M.D., D.D.S., AND ROBERT A. FOX, M.D.
ST. LOUIS

Billroth [1] coined the term "cylindroma" to designate a tumor which had arisen from the mucous glands of the accessory nasal sinuses and penetrated into the orbit. The tumor was characterized by a distinct parenchyma traversed by hyaline cylinders and tubes of stroma. In using the term "cylindroma" Billroth referred to the peculiar stroma rather than to the parenchyma. At first he regarded the cells of the parenchyma as epithelial, but a short time later he preferred to consider them as of connective tissue origin, precipitating a heated discussion as to the epithelial or the endothelial origin of the cylindroma. Although the endothelial concept seems to have been abandoned in favor of the epithelial one, there are still much confusion and lack of unanimity as to the genesis and the classification.

A large number of specimens of so-called cylindroma of the salivary and mucous glands have since been described as "mixed tumors." On the other hand, basically different neoplasms, such as true mixed tumors and adenoma, which occur in the region of the salivary glands and exhibit varying degrees of hyalinization, have been indiscriminately included in the cylindroma group. The occurrence of hyalinization in carcinoma with origin from salivary glands has led others to classify cylindroma as a variety of adenocarcinoma. The latter idea, propounded by McFarland [2] and by Mayo and Dockerty,[3] is supported by the "potential" malignancy of cylindroma. McFarland included cylindroma with the mixed tumors of the salivary glands, and stressed their generally unfavorable prognosis, particularly when subjected to surgical removal. He emphasized the "lack of correlation between the histopathology of the tumor and its clinical behavior" and expressed the belief that "the microscope, beyond showing that the lesion is a mixed tumor, is misleading." Mayo and Dockerty, in their first paper on cylindroma, also classified it with the mixed tumors of the salivary glands. They stated that "the average grade of malignancy was higher in the 'mixed tumor' group" and on this basis differentiated between the two types of growth. In a later study, however, they reported two "metastasizing adenocarcinomas of cylindroma type." They regarded them as "pure cylindromas" and warned against confusing this highly infiltrative neoplasm with the more common mixed tumor, which has a vastly different prognosis. Other authors, however, have refused to accept cylindroma as definitely a cancer.

In this paper we do not presume to be able to solve the question of the nature of these tumors. We are fully aware of the limitations of microscopic evaluation in this respect. Our study was conducted with the following questions in mind:

1. How does the homogeneous stroma of cylindroma develop and what is its relationship to the parenchyma?

2. From what is the parenchyma of pure cylindroma derived?

3. From the histologic point of view can pure cylindroma of the palate be considered as a variety of mixed tumor or as adenocarcinoma?

APPEARANCE OF THE TUMOR

The so-called cylindroma occurs wherever salivary or mucous glands are found. It forms slowly, is of elastic consistency and is usually freely movable beneath the mucosa or the skin. It tends to be sharply circumscribed. The cut surface of the tumor is grayish red and has a glossy, translucent, gelatinous appearance.

HISTOLOGY OF THE PALATAL GLANDS

In the submucosa of the posterior portion of the hard palate and especially in the soft palate there are dense aggregations of tubuloalveolar mucous glands. These are, for the most part, connected to secretory ducts of varying diameter, and to isthmuses between the glands and the main secretory ducts. The epithelium of the isthmuses and main ducts is composed of cells of two types: cylindric cells and the so-called bas-

From the Departments of Pathology of the Schools of Dentistry and Medicine of St. Louis University.

1. Billroth, T.: Virchows Arch. f. path. Anat. **17**: 357, 1859.

2. McFarland, J.: Surg., Gynec. & Obst. **63**:457, 1936.

3. Mayo, C. W., and Dockerty, M. B.: Surg., Gynec. & Obst. **74**:1033, 1942; Surgery **13**:416, 1943.

ket cells located between the cylindric cells and the basement membrane, as well as between the cylindric cells themselves. Detailed information regarding the structure of the basket cells can be found in an exhaustive study by Zimmermann.[4] In the parotid, submaxillary, sublingual and lacrimal glands the basket cells assume a stellate pattern because of radiating long threadlike extensions of the cytoplasm. In the mucotubular glands, however, they resemble fibroblasts because of their flat, broad spindle shape. Maximow and Bloom [5] and other investigators have considered these cells epithelial in origin and capable of contraction, a concept which induced Renaut [6] to call them "myoepithelial" cells. Their function is concerned with the expulsion of collected secretion within the glandular lumen. Because more force is required to extrude the sticky contents of the mucous glands as compared with the watery seroalbuminous contents of the albuminous glands, the former type contains far more basket cells than the latter. It is the basket cells, we believe, which play the important role in cylindroma of the mucous glands.

MATERIAL

Our histologic studies were confined to 3 tumors classified as cylindroma and 3 classified as adenocarcinoma of the palate. The specimens had been fixed in a 2 per cent solution of formaldehyde and embedded in celloidin (a concentrated preparation of pyroxylin). Detailed studies were limited to 1 particular specimen of cylindroma which was sectioned serially. This tumor of walnut size was singled out because it had been curetted two years prior to total excision. The curettement was done under the erroneous impression that the lesion was an abscess. In addition to the routine hematoxylin-eosin preparations, sections were studied with Mallory's aniline blue, Masson's trichrome and Best's congo red stain.

MICROSCOPIC FEATURES OF THE TUMORS STUDIED

The cytologic features of the tumors diagnosed as cylindroma varied considerably. Each of the growths was separated from the palatal epithelium by a remarkably thick, dense fibrous membrane (fig. 1). Generally, there was negligible round cell infiltration in the subepithelial stroma; it was most marked in the previously curetted tumor. Here the epithelium of the mucosa grew deep into the neoplasm, gradually infiltrating and intermingling with the parenchyma. The subepithelial fibrous membrane contained a moderate number of spindle-shaped cells and a few vessels with perivascular leukocytic infiltration. Sections stained with aniline blue according to Mallory's technic showed streaks of collagen fibrils arranged in whorls and strands, most of which were parallel to the epithelial surface. Radiating connective tissue septums divided portions of the tumor parenchyma into lobules (fig. 2). Although the connective tissue which extended between the lobules was composed of a moderate number of spindle cells centrally, the peripheral portions assumed a more homogeneous appearance. In addition the connective tissue stroma had invaded the individual glandular or ductlike structures of the parenchyma (fig. 2). It is especially noteworthy that the fibrous stroma had undergone hyaline degeneration wherever it was in contact with the secretion of the parenchymal cells (fig. 3). In sections stained with hematoxylin and eosin a bluish product of the epithelial cells formed a sort of membrane of varying thickness around dense areas of epithelium and branched into the interior between groups of cells. The connective tissue hyalin was pink and appeared to be fused with the epithelial secretion, forming an epithelial-mesenchymal substance. It seemed as though the epithelial secretion incited the hyalinization of the fibrous stroma. This transformation of the fibrous stroma also occurred when it invaded the ductlike structures and came into contact with the epithelial secretion (fig. 3). Special stains demonstrated the presence of elastin in the latter, but congo red failed to reveal amyloid, which Lubarsch [7] thought this homogeneous substance to be. There were areas entirely dominated by aggregations of this hyaline substance. The scanty remnants of degenerated cells within these areas furnished evidence that pressure had been exerted by the infiltrating stroma on the parenchyma. However, there was also evidence that the parenchyma had proliferated into the masses of hyaline substance. The larger homogeneous masses had a mottled pattern due to the presence of irregularly shaped lighter areas; the latter were the result of degeneration and disappearance of the tubular parenchyma (fig. 4).

The bulk of each tumor formed a spongy mass due to anastomosing branches of tubular structures of varying caliber (fig. 2). The tubules and the strands of cells could be traced to the normal mucous glands, with which they were connected by what may be called transitional structures. It was these areas which clearly

4. Zimmermann, K. W.: Die Speicheldrüsen der Mundhöhle und die Bauchspeicheldrüse, in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol. 5, pt. 1, pp. 61-244.

5. Maximow, A. A., and Bloom, W.: A Textbook of Histology, Philadelphia, W. B. Saunders Company, 1939.

6. Renaut, J.: Compt. rend. Acad. d. sc. **89**:247, 1879.

7. Lubarsch, O.: Virchows Arch. f. path. Anat. **122**:373, 1890.

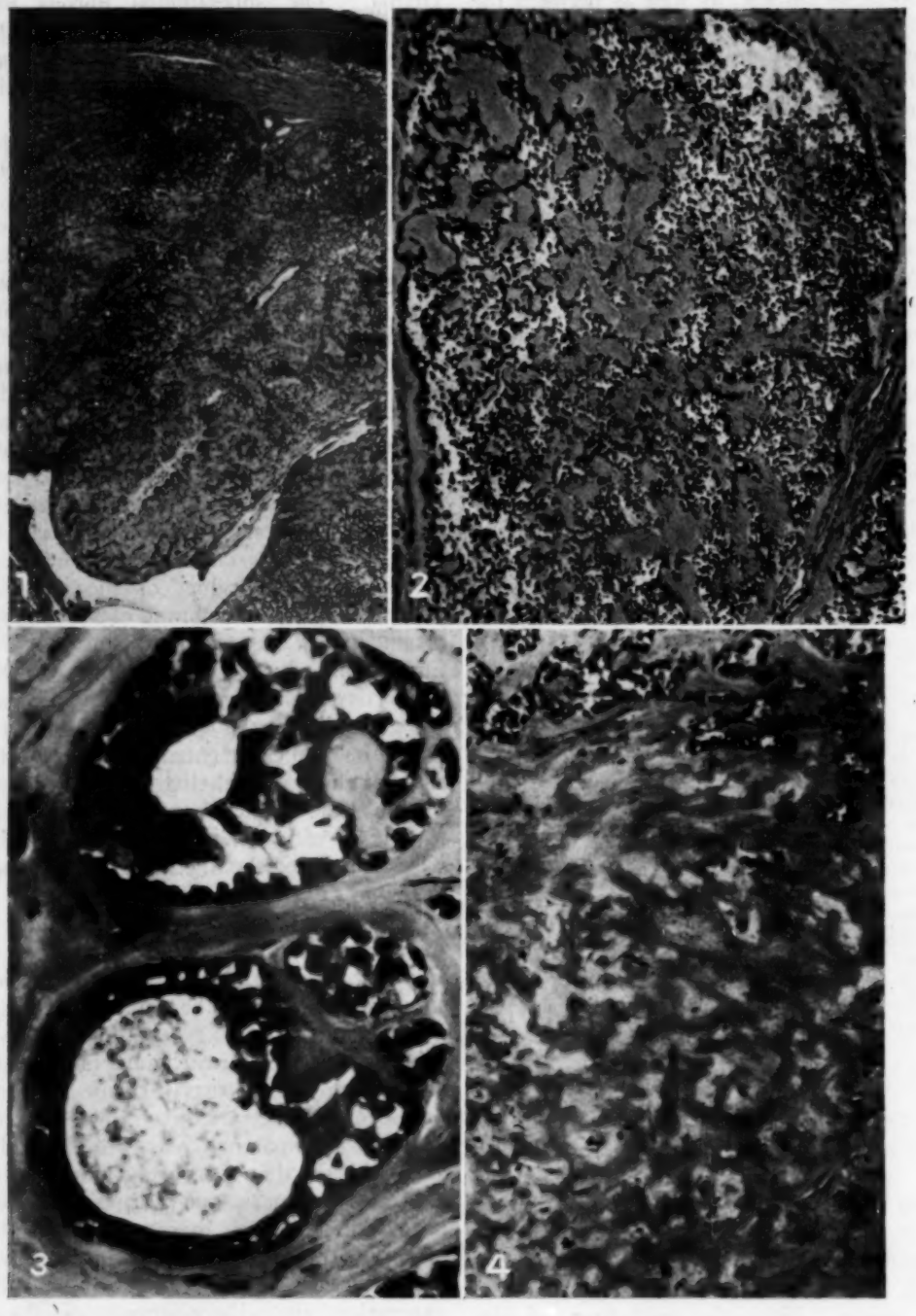


Fig. 1.—Cylindroma of the palate. An area of the tumor is shown, separated from the normal palatal mucosa by a fibrous wall. × 100.

Fig. 2.—Extensions of the fibrous wall dividing the tumor into lobes. Note the hyaline substance between and within tubes lined by epithelial cells. × 200.

Fig. 3.—Intercalated ducts from a transitional area between normal mucous glands and neoplasm. Proliferation of myoepithelial cells and invasion of stroma are shown. × 500.

Fig. 4.—Accumulation of hyaline stroma with irregular light patches, a result of the disappearance of myoepithelial cells following atrophy due to pressure. Cell remains are scattered throughout the field. × 200.

showed that the parenchymal cells of the tumor originated from the palatal mucous glands or their intercalated ducts. Proliferation of the secretory as well as of the basket cells had reproduced tubules or acini of mucous glands fairly well; the cells, however, appeared to be somewhat hyperplastic and occasionally degenerated (fig. 5). Excessive quantities of mucous secretion were observed occasionally, which had flattened or even caused complete disintegration, due to pressure, of the tubular lining cells. The lumens of the ductlike structures were surrounded and frequently obliterated by one or more layers of somewhat disfigured proliferating cylindric cells (fig. 3). The peripheral as well as the central proliferating cells extended into the

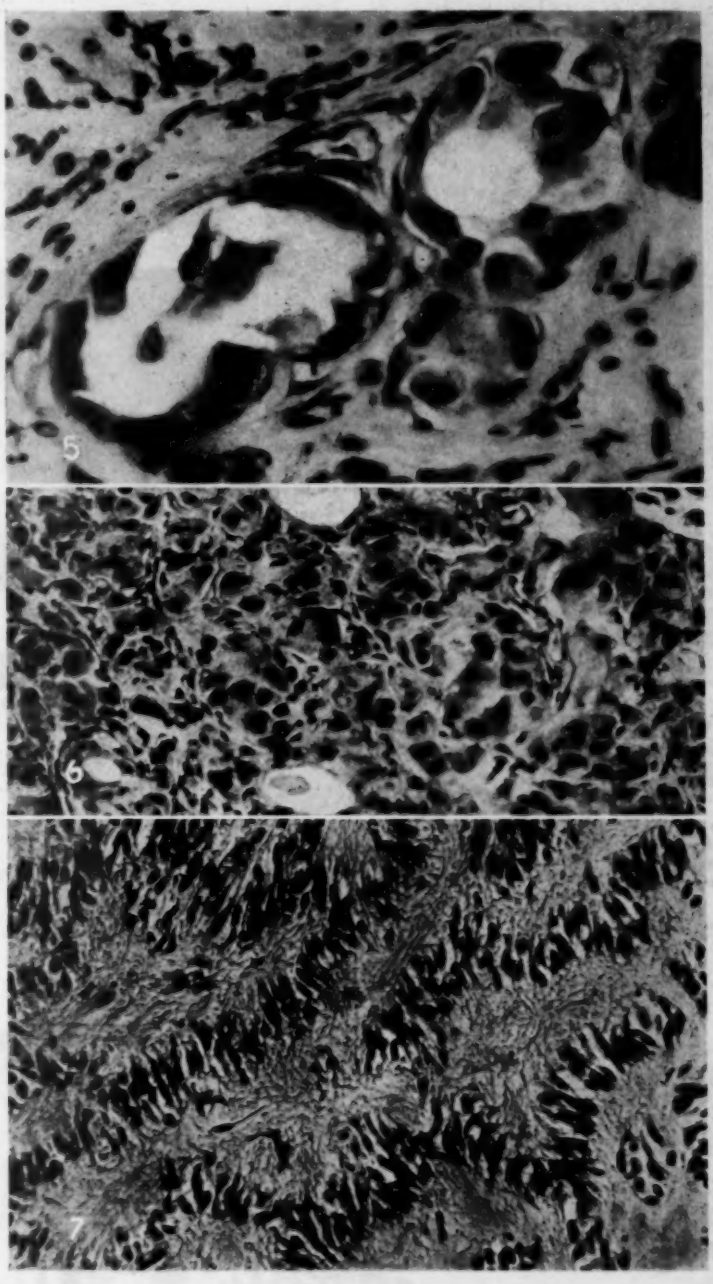


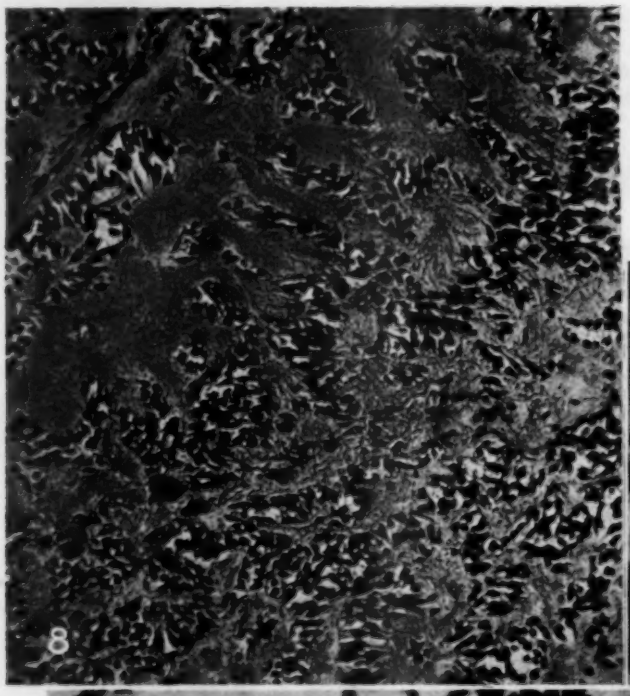
Fig. 5.—Tubules reproducing intercalated ducts. The inner layer of epithelial cells assumes a secretory function. Note the proliferating myoepithelial cells. × 500.

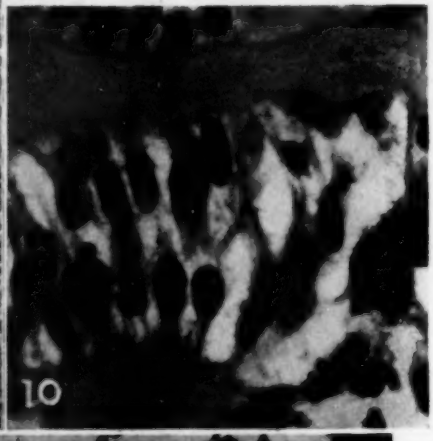
Fig. 6.—Adenomatous structure adjacent to the region of previous curettement. Note the pleomorphism and hyperchromatism of the lining cells. × 480.

Fig. 7.—Strands of myoepithelial cells in a collagenous stroma which has become hyalinized. Some cells are undergoing pressure atrophy. × 450.

stroma in solid cords to form pseudotubules filled with mucoid material, or cords of cells surrounding irregular spaces, some of which contained cellular debris.

which manifested striking polymorphism and hyperchromatism without mitotic figures (fig. 6). This tissue represented densely packed mucous gland isthmuses. Their lumens were





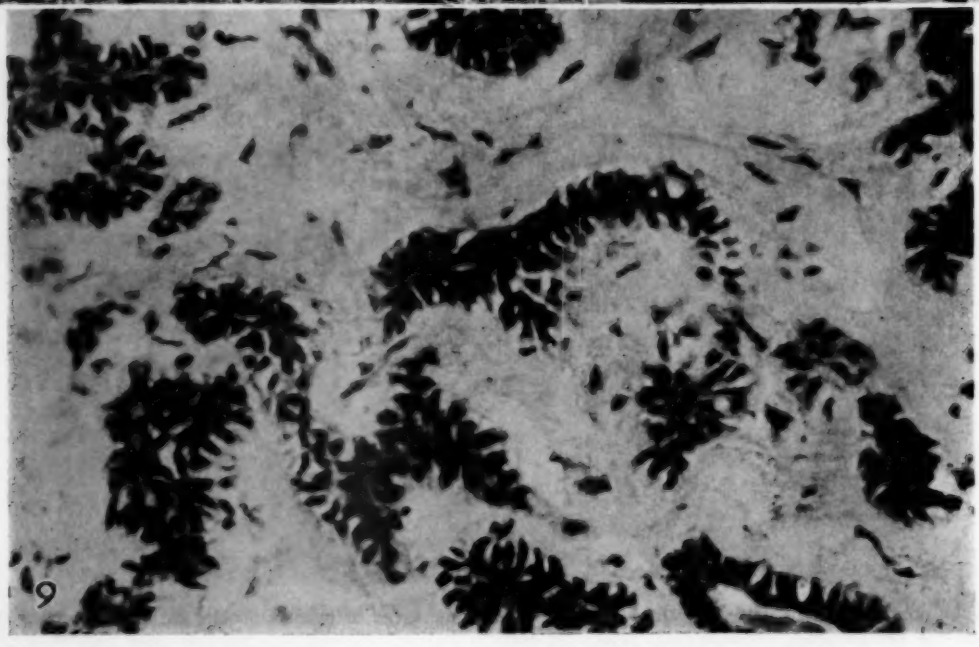


Fig. 8.—Hyalinization of fibrous stroma; proliferation of myoepithelial cells. × 400.

Fig. 9.—Network of tubules lined by a layer of flat epithelial and myoepithelial cells arranged like the needles of a pine tree. × 400.

Fig. 10.—Myoepithelial cells, the cytoplasm of which is fused with the hyaline stroma. × 600.

The secreting and the basket cells did not exhibit definite evidence of being cancerous. However, in the region of the former curettement there was a well defined adenomatous lobule

obliterated by either proliferating epithelial cells or mucus. Here and there the inner luminal lining cells principally, and the basket cells to a lesser extent, had undergone hyalinization and

keratinization. Giant epithelial cells with large, hyperchromatic, occasionally lobulated nuclei were found situated beside unusually small epithelial cells with pyknotic nuclei of varying degrees of chromatism. The picture resembled the lesions produced by Fischer-Wasels [8] in his studies of the effects of carcinogens on the parotid glands of rabbits and rats.

As stated before, the mass of each of our tumors consisted of strands or layers of proliferating myoepithelial cells (fig. 7 and 8). One neoplasm was composed almost entirely of ducts lined by a single layer of flattened epithelium, while the spindle or ovoid peripheral cells were arranged like the needles of a pine tree (fig. 9). Strands of similar spindle and ovoid cells were observed in another tumor; here they were separated by fibrous collagen which had been converted into a homogeneous hyaline substance in some places. The nuclei of these cells were remarkably large, variously shaped and rich in chromatin. There were no mitotic figures. Some cells had cytoplasmic processes which extended in several directions, giving them a stellate appearance, and joined them with each other. In other cells the cytoplasm was fused with the collagenous or hyaline stroma to such an extent that only the nucleus remained (fig. 10).

COMMENT

It appears from the microscopic examination of our material that cylindroma originates from the palatal mucous glands, with which it is connected by transitory structures. There was evidence of proliferation of the epithelial cells lining the intercalated ducts and especially of the basket or myoepithelial cells, located between the inner cylindric epithelial layer and the basement membrane. The bulk of each tumor was composed of interlacing strands and cords of basket cells arranged in an adenomatous pattern. The cytologic details cannot be fully understood unless one pays particular attention to the peculiar and intimate interrelation between the stroma and the parenchyma. We feel that both the stroma and the parenchyma develop a proliferating, invasive capacity of remarkable strength. However in this respect the evidence seems to indicate that the stroma is more powerful than the parenchyma, for it is the stroma which disrupts the epithelial aggregations and by pressure even produces atrophy. The epithelium, however, may regain its infiltrative power and again invade the wide expanse of stroma. The fibrous stroma, which originates from the well developed capsule, meets in its advance the epithelial secretion, which causes it to undergo hyaline degeneration. In those regions where there is no epithelial secretion the stroma maintains its fibrous character. Observations and conclusions similar to these were arrived at by Herzog [9] in 1921.

The secretion found in the ductlike structures of the tumors is the product of the cylindric lining cells. Zimmermann [4] proved that the inner cylindric cells, as well as the cuboidal cells of the intercalated ducts of the palatal mucous glands, can be converted into large mucus-secreting cells. If these lining cells diminish in size and their nuclei become smaller, their capacity to produce mucus vanishes.

We have emphasized repeatedly the significance of the basket or myoepithelial cells in the structure of these tumors. These cells and the odd relation between stroma and parenchyma, constitute the characteristic histologic feature. We cannot share the opinion of those authors who consider the hyaline stroma alone the main diagnostic feature, because there are many epithelial growths which exhibit wide stromal hyalinization.

Myoepithelial cells are found in the albuminous and mammary glands, as well as in the glands of Moll and the apocrine sweat glands. They are not directly connected to the stromal tissue which surrounds the acini and intercalated ducts but are separated from it by a basement membrane; although they do not leave their imprint on this membrane, they do on the acinous and cylindric cells of the ducts. As a rule, the cytoplasm contains fibrils which pass through the large dark nucleus. However, we observed that wherever myoepithelial cells appear in close proximity to hyalinized stroma, the fibrillar cytoplasm also becomes hyaline, thus fusing itself with the stroma. In sections stained with hematoxylin and eosin these cells are elongated and have large hyperchromatic nuclei. The Masson stain, however, brings out a reddish cytoplasm, which helps to differentiate myoepithelial from secretory epithelial cells.

The importance of the myoepithelial cell was recognized a long time ago. Ribbert [10] and others demonstrated the ability which these cells have to proliferate after ligation of the excretory duct of the parotid gland of the rabbit or in inflammatory and regenerative processes involving that gland. Some authors regarded them as

8. Fischer-Wasels, B.: Allgemeine Geschwulstlehre, in Bethe, A.; von Bergmann, G., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 14, p. 1477.

9. Herzog, G.: Beitr. z. path. Anat. u. z. allg. Path. **69**:422, 1921.

10. Ribbert, M. W.: Sitzungb. d. nied.-rhein. Gesellsch. f. Nat. u. Heilk., 1879, p. 86.

germ cells of the secreting glandular epithelium, and Krompecher [11] called them "basal cells." In his studies of epithelioma of salivary and mucous glands Krompecher referred to a "reticular mucous cylindroma" which was composed of proliferated "basal cells" as a "basal cell adenoma." The tumors of the parotid gland described by French and German pathologists as acinous and canalicular adenoma must not be confused with Krompecher's "basal cell adenoma."

Sheldon [12] observed proliferation of myoepithelial cells in tumors of the sweat glands, and Kuzma [13] described proliferating elongated contractile cells in the human breast.

Recently, Sheldon [14] in an elaborate study of 54 tumors of the salivary glands divided his material into four groups. He regarded the tumors in the first group as adenoma derived from the secreting epithelium of the salivary glands. His second group was constituted of the "mixed tumors" because "in addition to the secreting epithelium, the basket cells, which are a normal component of the salivary glands, contribute not only to the tumor but are actually the predominating cells." He held that the normal picture is further distorted by "degeneration of the epithelium with subsequent myxomatous and pseudocartilaginous appearance of the stroma. In addition, squamous metaplasia of the epithelium may occur. True cartilage or bone which arises by metaplasia from the connective tissue stroma further confuses the picture." The tumors of the third group were characterized by basket cells alone without degenerative or metaplastic changes of the stroma. Sheldon suggested the name "myoepithelioma" for these slowly invading growths. The fourth group was composed of tumors diagnosed as carcinoma of the secretory epithelium.

The tumors classified as cylindroma of the palatal mucous glands which we examined do not fit into Sheldon's second group ("mixed tumors") because of the absence of myxomatous, pseudocartilaginous tissue and squamous metaplasia, as well as of cartilage and bone. On the other hand, they cannot be placed in his third group because, though their bulk consists principally of myoepithelial cells, there are also adenomatous structures resembling normal mucous glands. The interlacing network of strands of proliferating myoepithelial cells in a hyalinized stroma of epithelial-mesenchymal origin associated with adenomatous formations of secreting cells induces us to suggest the term "adenomyoepithelioma" for these tumors of the palatal mucous glands. The absence of definite microscopic features of cancer delimits adenomyoepithelioma (cylindroma) from adenocarcinoma of the palate. However, we believe that though the growth is principally noncancerous, it may undergo transformation into adenocarcinoma. This alteration may develop spontaneously or may be encouraged by surgical intervention. However, if one wishes to retain the term "cylindroma," we should prefer to consider the cancerous growth as carcinomatous cylindroma rather than as cylindromatous carcinoma.

11. Krompecher, E.: Beitr. z. path. Anat. u. z. allg. Path. **70**:489, 1922.
12. Sheldon, W. H.: Arch. Path. **31**:326, 1941.
13. Kuzma, J. F.: Am. J. Path. **19**:473, 1943.
14. Sheldon, W. H.: Arch. Path. **35**:1, 1943.

SUMMARY

Cylindroma of the palate arises from the cells lining the intercalated ducts of the palatal mucous glands. Not the cylindric cells but the basket or myoepithelial cells chiefly form the bulk of the parenchyma of this tumor. There is an intimate relationship between the erstwhile cylindric cells which differentiate into secreting mucous cells and the fibrous connective tissue stroma which radiates from the well preserved capsule into the parenchyma. We believe that the fibrous stroma invades the tubular epithelial formations and by coming into contact with the secretion of the latter becomes converted into a hyaline substance.

Although this tumor of the mucous glands may be remotely related to the "mixed tumors" we interpret it as a specific type of neoplasm. The name "adenomyoepithelioma of the palatal mucous glands" seems to be appropriate. The tumor though genuinely benign may undergo cancerous alteration.

EXPERIMENTAL NEPHROPATHIES

I. A METHOD OF PRODUCING CONTROLLED SELECTIVE INJURY OF RENAL UNITS BY MEANS OF CHEMICAL AGENTS

JAMES P. SIMONDS, M.D., AND OPAL E. HEPLER, M.D.
CHICAGO

In his comprehensive review of experimental nephropathies in 1937, Horn [1] remarked that "the abnormalities reported following the use of chemical agents and irradiation have but a remote application to the human disease. . . . The value of such procedures resides more significantly in the pursuit of functional and toxicologic studies." Most of the contributors to the extensive literature on the effects of chemical agents on the kidneys have not differentiated between these two points of view. Usually, investigators have been more concerned with the certainty of damaging the kidneys than with producing a selective effect by the use of the poison. The dose employed was not, therefore, adapted to the requirements of an accurate study of renal function.

One of the chief difficulties that has confronted the experimental pathologist in this field has been the lack of dependable means of identifying the particular portion of the renal tubule damaged by a chemical agent. Suzuki [2] and Aschoff and Suzuki [3] used the vital dye phenol red to differentiate the three parts of the proximal convoluted tubule. Edwards [4] macerated portions of kidneys injured with mercury bichloride, dissected them with glass needles under a microscope and towed the isolated tubules to an area of the dish used in dissection, where it was uncoiled as far as possible in order to identify the different segments. Both of these methods are tedious, time consuming and difficult. In the course of our studies during the past seven years on the effects of chemical agents on the kidneys of dogs we have developed a method by which the first and the terminal portion of the canine renal tubule can be selectively injured with considerable accuracy and later identified in microscopic sections with reasonable certainty.

DESCRIPTION OF METHOD

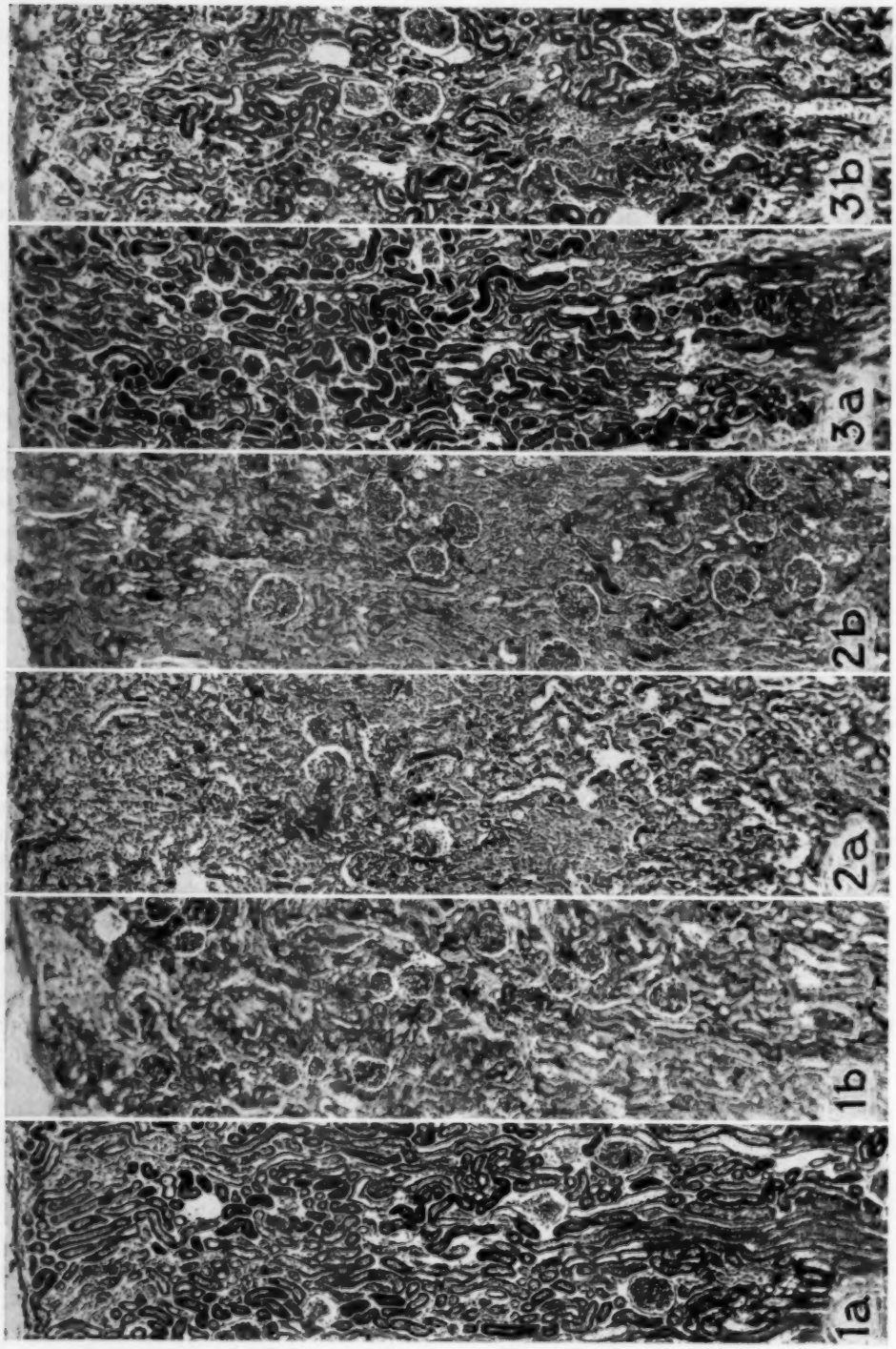
Each dog was weighed and its total blood volume was determined approximately by the formula: weight in grams $\times$ 0.0925 — blood volume in cubic centimeters. Then a carefully measured quantity of the poison in isotonic solution of sodium chloride was slowly injected intravenously. The amount administered ranged from 0.10 to 3.0 mg. per hundred cubic centimeters of blood. At proper intervals, usually from eighteen to seventy-two hours, the animals were killed and their kidneys studied microscopically with the aid of several staining methods.

In our experiments potassium dichromate, mercury bichloride and uranyl nitrate were used as renal poisons. Suzuki [2] was one of the first to present evidence, based on more accurate methods of differentiating the parts of the proximal convoluted tubule, that the dichromate affects the first part, while the bichloride and uranyl nitrate injure particularly the terminal portion. This claim has been frequently disputed. Recently, Edwards [4] insisted that the bichloride does not cause necrosis of the terminal portion of the proximal convoluted tubule. He used rabbits, guinea pigs, rats and frogs in his experiments. The following comments on the work of Edwards are pertinent: In the first place, he teased out an individual tubule from macerated renal tissue and identified the affected portion of the tubule by its thinness. For purposes of identification and description he divided each tubule into eight (presumably equal) segments. In the second place, the poison was administered intraperitoneally (except in the frogs), and the total dose per kilogram of body weight was much higher than that used in our experiments—ranging in the rabbits from 2.44 to 5.88 mg. per kilogram. Furthermore, Edwards found a significant species difference in the distribution of the necrosis in the kidneys of the

From the Department of Pathology, Northwestern University Medical School.

This investigation was aided by a grant from the Committee on Therapeutic Research of the American Medical Association.

1. Horn, H.: Arch. Path. **23**:71 and 131, 1937.
2. Suzuki, T.: Morphologie der Nierensekretion unter pathologischen Bedingungen, Jena, G. Fischer, 1912.
3. Aschoff, L., and Suzuki, T.: Verhandl. d. deutsch. path. Gesellsch. **15**:199, 1912.
4. Edwards, J. G.: Am. J. Path. **18**:1011, 1942.



Figures 1, 2 and 3.

EXPLANATION OF FIGURES 1, 2 AND 3

Fig. 1.—Renal tissue of dogs poisoned with potassium dichromate ($K_2Cr_2O_7$). (*a*) Three doses of 1 mg. each of the poison per hundred cubic centimeters of blood were given to dog K Cr 1 on three successive days. The animal was killed on the fourth day after the first dose. Necrosis is seen to be limited to the subcapsular zone and to the labyrinth; none is present in the straight terminal portions of the proximal convoluted tubules. × 55. (*b*) Four milligrams of the poison per hundred cubic centimeters of blood was given to dog K Cr 8. The animal was killed on the third day. Marked necrosis may be seen in the subcapsular zone and labyrinth. Some necrosis is present in the straight portions of the proximal convoluted tubules. × 55.

Fig. 2.—Renal tissue of dogs poisoned with mercury bichloride ($HgCl_2$). (*a*) One dose of 3 mg. of the poison per hundred cubic centimeters of blood was given to dog K Hg 8. The animal was killed on the fourth day. No necrosis is present in the subcapsular zone. Marked necrosis may be seen in the straight terminal portions of the proximal tubules near the center of the photomicrograph. × 55. (*b*) The same dose of this poison was given to dog K Hg 6. The animal was killed on the third day. Necrosis is more extensive than in dog K Hg 8. This illustrates the individual differences in susceptibility of different dogs when fairly large doses are administered. × 55.

Fig. 3.—Renal tissue of dogs poisoned with uranyl nitrate ($UrO_2[NO_3]_2$). Two doses of 1 mg. each of this poison per hundred cubic centimeters of blood were given to dog K Ur 1. The animal was killed on the third day. Necrosis is not present in the subcapsular zone or in the labyrinth. Necrotic straight terminal portions of the convoluted tubules are seen in the lower part of center. × 55. (*b*) Three doses of 1 mg. each of the same poison per hundred cubic centimeters of blood were given to dog K Ur 2 on successive days. The animal was killed on the fourth day. Slight necrosis is seen in the subcapsular zone and labyrinth; marked necrosis, in the straight terminal portion of the proximal convoluted tubules in the lower part of the photomicrograph. × 55.

mammals used by him. In the rat the necrosis was most frequently observed in the fifth and sixth segments; in the rabbit, in the sixth and seventh segments, while in the guinea pig it extended from the eighth segment upward for varying distances, even to the point of junction of the tubule with the glomerulus. The animals used by Edwards survived for periods ranging from less than one day to one hundred and thirty-four days.

It is of particular interest that, as demonstrated by Edwards, the location of the maximal injurious action of mercury bichloride in the proximal convoluted tubules varies in different species of animals. Our experiments were limited entirely to dogs. When minimum necrotizing doses of the chemical agents are injected intravenously into dogs, potassium dichromate causes necrosis of the first part, and mercury bichloride and uranyl nitrate of the terminal portion, of the proximal convoluted tubule. This can be demonstrated in dogs by two quite simple devices.

1. In the kidneys of dogs and other mammals there is a narrow zone immediately beneath the renal capsule which is devoid of glomeruli. This zone is composed almost entirely of the first portions of proximal convoluted tubules which come off from the more superficial, or peripherally located, glomeruli, with a few distal convoluted tubules. In the kidneys of dogs poisoned with the smallest necrotizing dose of potassium dichromate, necrosis was present in this narrow subcapsular zone (fig. 1 *a*). In the deeper portions of the cortex, the necrosis was in the labyrinth and involved transverse or sharply curved short sections of tubules, which were probably segments of the first portions of the proximal convoluted tubules of glomeruli situated more deeply in the cortex. The straight, terminal portions of these tubules, which lie chiefly in the outer part of the labyrinth along the margins of the medullary rays, were not necrotic when the dose was properly selected. Larger but still very small doses caused more extensive necrosis (fig. 1 *b*). On the other hand, in the kidneys of dogs poisoned with the minimum necrotizing dose of mercury bichloride or of uranyl nitrate, necrosis was not seen in the narrow subcapsular zone but was present in the straight terminal tubules deep in the cortex along the margins of the labyrinth (figs. 2 *a* and 3 *a*). With equivalent doses, the necrosis caused by mercury bichloride seemed to extend farther upward into the proximal convoluted tubules than did that caused by uranyl nitrate. A possible reason for this difference will be discussed in a later paragraph. Slightly larger doses of these substances also caused more widespread necrosis (figs. 2 *b* and 3 *b*).

2. In sections of the kidneys of dogs stained with sudan III we repeatedly noted the presence of fat in tubules that lay in the zone of junction between the labyrinth and the medullary rays (fig. 4). The transition from fat-free to fat-containing epithelium in a tubule may be quite abrupt. Later we found that Modell[5a] had made a similar observation and had stained isolated tubules dissected out of macerated kidneys of dogs and cats. He found by this means that the fat was present in the straight, terminal portion of the proximal convoluted tubule of the dog and in higher segments in the kidneys of cats. Modell's observations were confirmed and corrected by Foote.[5b] It seemed, therefore, that fat in this location in normal canine kidneys might be used to identify the lower or terminal portions of the proximal convoluted tubules. We studied sudan-stained sections of the kidneys of 163 dogs in order to determine what percentage of them contained fat. This group contained normal controls and dogs that had been poisoned with various substances. The results were surprising. For purposes of classification these kidneys were divided into two groups: (*a*) those in which the epithelium of the terminal portions of the proximal tubules contained sufficient fat for satisfactory identification and (*b*) those in which fat was either not present or present in such small amount that it could not serve the purpose of identification of parts of the tubules.

Presence of Fat in Terminal Portions of Proximal Convoluted Renal Tubules of Dogs Given Various Poisons

	Fat Not Sufficient for Identification, per Cent	Fat Sufficient for Identification, per Cent	Number of Dogs
Snake venom	75.0	25.0	20
Streptococcus toxin	50.0	50.0	6
Diphtheria toxin	47.8	52.2	23
Normal controls	45.2	54.8	42
Staphylococcus toxin	41.7	58.3	12
Mercury bichloride	23.5	76.5	17
Potassium dichromate	14.4	85.6	21
Uranyl nitrate	9.1	90.9	22
			163
Classified summary of results			
Glomerular poisons	55.7	44.3	61
Normal controls	45.2	54.8	42
Tubular poisons	15.0	85.0	60
			163

The results are shown in the accompanying table. The classified summary at the end of the table is of particular interest. More than half of the normal control dogs had sufficient fat in the terminal portions of their proximal convoluted tubules to permit identification of these

5. (*a*) Modell, W.: Anat. Rec. **59**:253, 1934. (*b*) Foote, J. J.: Proc. Soc. Exper. Biol. & Med. **34**:196, 1936.

structures. Recognition of the fact that a specific part of the tubule of the normal canine kidney may contain fat in appreciable and even in considerable amount may aid in avoiding an incorrect interpretation of the results of experimental procedures on these organs. However, the type of poison used does appear to have a definite effect on the quantity of fat found in the tubular epithelium.

The venom of snakes (moccasin and rattlesnake) and the toxins produced by streptococcus, staphylococcus and the diphtheria bacillus are all proteins and therefore colloids, although their molecules are small in comparison with those of some of the proteins. Colloids do not pass readily through the glomerular filter and tend to become concentrated in the capillaries because of the loss of water by filtration. It is for this reason that these substances have been classed as glomerular poisons. It will be noted that the kidneys of the dogs to which these poisons were administered contained somewhat less fat than did those of the normal controls. The difference (about 10 per cent) may not be sufficient to be significant.

Mercury bichloride, potassium dichromate and uranyl nitrate are crystalline substances and therefore pass easily through the glomerular filter. By absorption of water from the glomerular filtrate, they are concentrated in the tubules. Since their most evident effect is on the tubular epithelium they have been classed as tubular poisons in the table. Eighty-five per cent of the kidneys of this group of dogs contained sufficient fat to identify the straight terminal portions of the proximal convoluted tubules. The difference between this group and the normal controls (about 30 per cent) is statistically significant. It appears, therefore, that these tubular poisons increase the tendency of the specific tubular epithelium of dogs to accumulate fat and thus aid in identification of the part of the tubule involved.

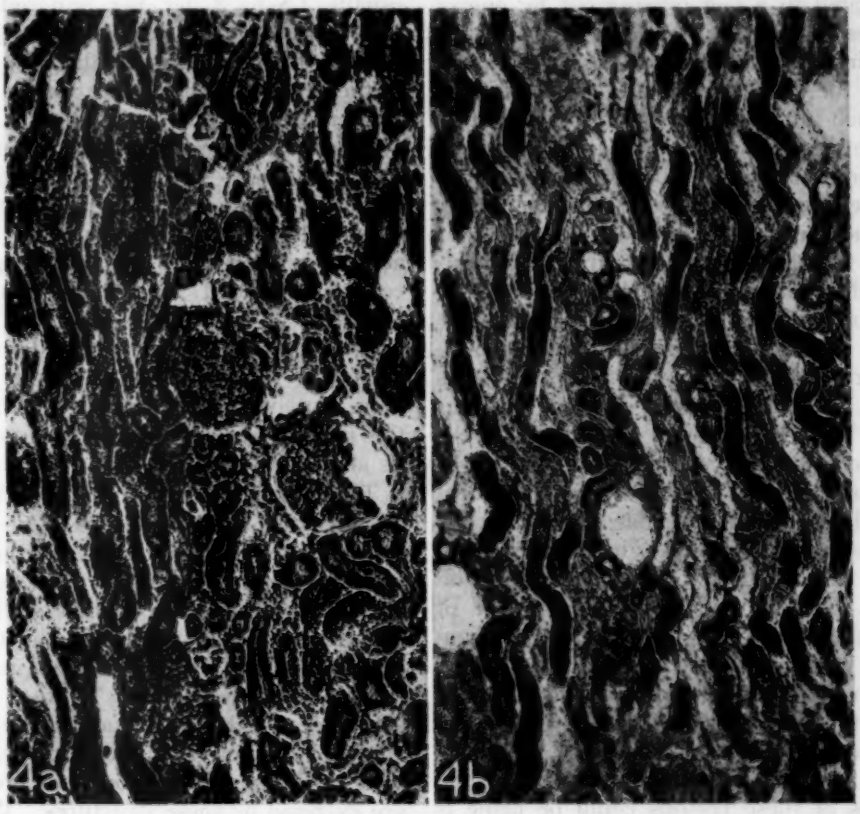


Fig. 4.—Renal tissue of dogs poisoned with mercury bichloride ($HgCl_2$) and potassium dichromate ($K_2Cr_2O_7$). (*a*) One milligram of mercury bichloride per hundred cubic centimeters of blood was given to dog K Hg 3. The animal was killed on the fourth day. Sudan III stain was used. Fat, reproduced as black droplets, is seen in the straight terminal portions of the proximal convoluted tubules. (*b*) One dose of 4 mg. of potassium dichromate was given to dog K Cr 8. Sudan III stain was used. Many of the cells containing fat are necrotic.

These two methods of identifying the first and the terminal portions of the proximal convoluted tubules can be applied only if the minimum necrotizing dose of the poison is administered. When in a dog, after the injection of a properly selected dose, the necrosis of tubular epithelium is found to be limited to the sub-

capsular, aglomerular zone and to the labyrinth, leaving the straight, fat-containing, terminal portion without visible damage, that poison may be said to affect the first segment of the proximal convoluted tubule. When, on the other hand, after such an injection the necrosis is found to be limited to the straight, fat-containing, terminal portion, leaving the subcapsular zone intact, that poison may be said to have affected the terminal segment of the proximal tubule.

Aside from possible differences in relative toxicity, an explanation of the involvement of different parts of the proximal convoluted tubule may be related to a fact pointed out by one of us in another connection.[6] Presumably it is the metal ions in the molecules of each of the poisons that injure the renal epithelium. It is assumed also that such a metallic poison in weak solution can damage the cells only by entering them and that the amount entering the cells is proportional to the concentration of the poison in the tubular lumen. The concentrations of the metallic ions in each of the three poisons used in these experiments differ among themselves. One milligram of potassium dichromate contains 6.80×10^{-3} gram atoms of chromium; 1 mg. of mercury bichloride contains 3.66×10^{-3} gram atoms of mercury, and 1 mg. of uranyl nitrate contains 2.53×10^{-3} gram atoms of uranium. If the absorption of water proceeds uniformly throughout the proximal convoluted tubules, a concentration of chromium ions capable of injuring the renal epithelium would be attained at a higher level in the tubules than would the concentration of metallic ions with a corresponding dose of either of the two other poisons. Potassium dichromate would therefore be expected to damage a portion of the proximal convoluted tubules nearer to the glomerulus than would either mercury bichloride or uranyl nitrate.

Perhaps a more accurate comparison of the toxic effects of these poisons could be made if the amount of each substance injected was proportional to the gram atom equivalent of the respective metal in the molecule than if merely an equal number of milligrams was used, as was done in these experiments. This would certainly be necessary if one had to determine the relative toxicity of the three substances.

Except for minor variations due to individual differences in susceptibility to one or another of the poisons used in these experiments, the degree of injury of the tubular epithelium varies with the quantity of poison administered. For this special reason and for more general reasons microscopic examination of the kidneys of treated animals is essential to a correct interpretation of the results of experiments on renal function based on the use of such agents. More than 3 mg. per hundred cubic centimeters of blood of any of the substances used in these experiments will produce necrosis throughout the greater portion of the proximal convoluted tubule. With the smallest necrotizing dose—usually 1.5 to 2 mg. per hundred cubic centimeters of blood—potassium dichromate causes necrosis that is sharply localized in the first part of the proximal convoluted tubule, and mercury bichloride and uranyl nitrate, in the terminal portion. With smaller subnecrotizing doses, visible damage—swelling and splitting of the epithelium—can be detected in that portion of the tubule in which the particular poison characteristically produces its necrotizing effect. The conclusion would seem to be justified, therefore, that an extremely small dose, incapable of producing visible injury, would induce disturbances of function that would be limited even more closely to that part of the tubule in which the particular poison in larger doses produces its characteristic necrosis.

This method of controlled selective injury of specific parts of the nephrons by properly chosen doses of chemical substances, adequately checked by microscopic examination of the kidneys, lends itself to more accurate studies of the functional activities of these organs than methods heretofore employed. It should be of value in determining the mechanisms of the clearance of substances, such as urea and dextrose, that are absorbed by the renal tubules, and of substances, such as diodrast and exogenous creatinine, that are excreted by these structures. We have used this controlled method in studies of the clearance of urea, endogenous creatinine, inulin and diodrast in dogs. The results will be published in another paper.

SUMMARY

Controlled selective injury of specific parts of the renal units may be produced by means of chemical agents and the part of the proximal convoluted tubule affected identified. This may be applied in the study of renal function.

6. Simonds, J. P.: J. A. M. A. **120**:786, 1942.

Case Reports

MYELOMALACIA OF THE CERVICAL PORTION OF THE SPINAL CORD, PROBABLY THE RESULT OF ROENTGEN THERAPY

LEWIS D. STEVENSON, M.D., AND ROBERT E. ECKHARDT, M.D., PH.D., NEW YORK

The side effects of roentgen therapy are principally: (*a*) direct injury to the cells as evidenced by necrosis, vacuolation of the cytoplasm and abnormal mitoses; (*b*) vascular changes, characterized by endothelial thickening and proliferation, with resultant thrombosis, and degeneration of the elastica and the muscle cells of the media; (*c*) hyalinization of the collagen.[1] These changes occur in all tissues, including those of the central nervous system. However, it is the vascular change which seems to offer the most serious complication of radiation therapy directed to the central nervous system.[2] It has been our experience to observe a man believed to have a metastasis of lymphoepithelioma of the nasopharynx after intensive roentgen therapy to the neck and the oropharynx. Postmortem examination revealed not the expected metastasis but myelomalacia probably secondary to vascular changes from the radiation therapy.

REPORT OF A CASE

F. K., a 43 year old Turkish waiter, when first seen in the New York Hospital Clinic, on Sept. 29, 1941, complained that he had noted a painless swelling of the left side of the neck for three months. He gave a history of having had syphilis for fifteen years, previously treated for four months by injections made in the hip and the arm. On the left side was a firm, nontender, freely movable postauricular node, 3 by 2 by 2 cm., and on the right some smaller (0.5 cm.) firm, nontender freely movable posterior cervical nodes. Careful examination of the nasopharynx, with the patient under local anesthesia, revealed a 1.5 cm. grayish-covered area to the left of the midline. The Kline test was negative. Biopsy of this lesion revealed lymphoepithelioma. Roentgen therapy was given through five portals as outlined in the accompanying table. This first course of therapy was given from Oct. 21, 1941 to Jan. 2, 1942.

This exposure was followed by complete disappearance of the lesions. The patient complained only of dryness of the pharynx and the nasal passages, an inevitable result of the radiations he had received. In November 1942 a necrotic area developed in the midline of the posterior part of the hard palate, which responded to local irrigations.

He was examined at approximately three month intervals thereafter. On Sept. 8, 1943, a 2 cm. node was found lying in the soft tissues over the insertion of the right sternocleidomastoid muscle. To this node he received 4,500 r (15 × 300 r) with 200 kilovolts, 15 milliamperes, at 50 cm. target skin distance and with a filter of 0.5 mm. of copper and 1 mm. of aluminum. The node disappeared, and an ulcer of the skin over the site healed promptly. In the early part of November he began to notice stiffness in the left arm and the left leg, and when this progressed to the point where he was no longer able to carry on his work, he was admitted to the hospital, December 29. On admission he said that he had first noted jumping of the left leg while riding in the subway train or sitting with his legs crossed. This was followed by stiffness and clumsiness of the left arm and the left leg. He became constipated and found that on three occasions he had urinated involuntarily. His penis felt dead, and he had become impotent. General physical examination disclosed nothing remarkable except for induration of the tissues of the neck in the region of the previous radiation therapy. Roentgen examination of the chest revealed only apical pleural thickening and mild emphysema. Neurologic examination revealed hyperreflexia of the left side, left finger stretch, absence of abdominal reflexes of the left side and a Babinski sign on that side. There was marked motor weakness of the left side, not including the face. These signs were interpreted as indicating disease of the left corticospinal tract below the head.

Reexamination three days later showed that a finger stretch and a Babinski sign had appeared on the right side, that sensation to pinprick was lost below the third thoracic segment bilaterally, that sensation of heat was

Roentgen Treatments

Portal	Location	Size, Cm.	Treatments	Factors: Kilovolts	Factors: Milliamperes	Factors: Target Skin Distance, Cm.	Filters, Mm.	Total r
A	Intraoral	2.5 around	10 × 400 r	200	15	40	0.5 Cu + 1 Al	4,000
B	Right temporal	6 around	16 × 250 r	200	15	50	1 Cu + 1 Al	4,000
C	Left temporal	6 around	16 × 250 r	200	15	50	1 Cu + 1 Al	4,000
D	Right cervical	13 × 6	16 × 250 r	200	15	50	1 Cu + 1 Al	4,000
E	Left cervical	12 × 9	23 × 250 r	200	15	50	1 Cu + 1 Al	5,750

From the departments of pathology and medicine of the New York Hospital and the Cornell University Medical College.

1. Warren, S.: Physiol. Rev. **24**:225, 1944.

2. Warren, S.: Arch. Path. **35**:127, 1943.

lost below the fourth cervical segment bilaterally but that sensation of touch was normal throughout. Lumbar puncture showed clear spinal fluid under an initial pressure of 100 mm. of water. Manometric findings were normal. The protein was 42 mg. per hundred cubic centimeters; the cell count, 0; the colloidal gold curve, 1122111100, and the Wassermann reaction of the spinal fluid, negative. The urine and the blood count were unremarkable, and the Mazzini flocculation test of the blood for syphilis was negative. An electroencephalogram showed a normal record, class II-I.

It was felt that these abnormalities might rise from a rapidly expanding intramedullary lesion in the region of the fourth cervical segment, possibly a metastasis. Cervical laminectomy was therefore performed and the cervical part of the cord explored on Jan. 5, 1944. The cord and the dura from the sixth cervical vertebra to the foramen magnum appeared normal, with no evidence of epidural or intramedullary growth and no apparent vascular changes.

Following operation there was no improvement in this man's condition; rather the signs and symptoms progressed to include both sides, and complete urinary incontinence developed. Since it was thought that the laminectomy had ruled out late radiation fibrosis and adhesive arachnoiditis of the cord, a course of roentgen therapy was directed to the cervical cord for the possible effect on any undisclosed metastasis. Through an 8 cm. portal in the posterior cervical region 3,300 r (11 × 300 r), with 200 kilovolts, 15 milliamperes at a 50 cm. target skin distance and with a filter of 0.5 mm. of copper and 1 mm. of aluminum, was given.

Despite the therapy the patient's condition became progressively worse. He had increasing difficulty clearing mucus from his throat, a left-sided headache developed, and there was evidence of paralysis of the intercostal muscles with signs of atelectasis and bronchopneumonia in both lungs. On Feb. 24, 1944 he died, apparently of respiratory paralysis, oxygen and morphine being of no avail.

Autopsy.—There was 100 cc. of serous fluid in each pleural cavity. There were scattered areas of consolidation in all lobes, particularly in the upper lobe and both lower lobes of the right lung. There were large areas of fibrous pleural thickening over both upper lobes.

Fig. 1.—Section of the cervical region of the spinal cord stained for myelin. It shows extensive demyelination and areas of necrosis.

An increased amount of cerebrospinal fluid was noted in the meninges.

The bony trabeculae of the vertebrae were slightly softer than usual. The marrow was gray-red.

Microscopic Observations.—The lungs showed patchy areas of consolidation with alveolar edema fluid and cells which were mainly polymorphonuclear.

No tumor cells were seen in the nasopharynx. Tissue from the region of the laminectomy revealed atrophy of muscle fibers and proliferation of muscle sheath cells, with formation of mononuclear giant cells and

ductlike structures that in places simulated a true gland. No tumor cells were seen. Several sections including bone and soft tissue showed profound injury compatible with that produced by roentgen rays, with atrophy of bone marrow and foci of necrosis, and perivascular infiltrations, but no thrombosis of vessels.

The vertebral marrow was infiltrated in large areas by epithelial cells with collections of lymphocytes, conforming with the diagnosis of lymphoepithelioma.

Sections through the cervical region of the spinal cord, stained for myelin sheaths, showed extensive loss of myelin in the anterolateral columns of both sides, somewhat more marked on one side than on the other. There was also considerable loss of myelin in the posterior columns of the spinal cord. In the demyelinated areas a number of small necrotic foci were present (fig. 1). The meninges were normal. Sections of the same region stained by the trichrome method showed extensive changes in the blood vessels of the white matter and the gray matter. These changes for the most part were fibrous thickening of the smaller arteries and arterioles with considerable narrowing of the lumens of these vessels (fig. 2). About some of the vessels, a few lymphocytes were present in the perivascular spaces, and an occasional mononuclear cell was present in the adventitial coat of the artery. Sections stained with hematoxylin and sudan III showed the demyelinated areas to be densely packed with cells containing fat. There was an excessive amount of fat in many of the cells of the anterior horns. The cells of the anterior horns were reduced in number, and some of them showed vacuolation and other degenerative changes. There was little reactive gliosis in the demyelinated areas or elsewhere. Sections of the cord in the thoracic and lumbar regions showed no such vascular changes but merely wallerian degeneration of the descending pathways—chiefly of the pyramidal tract.

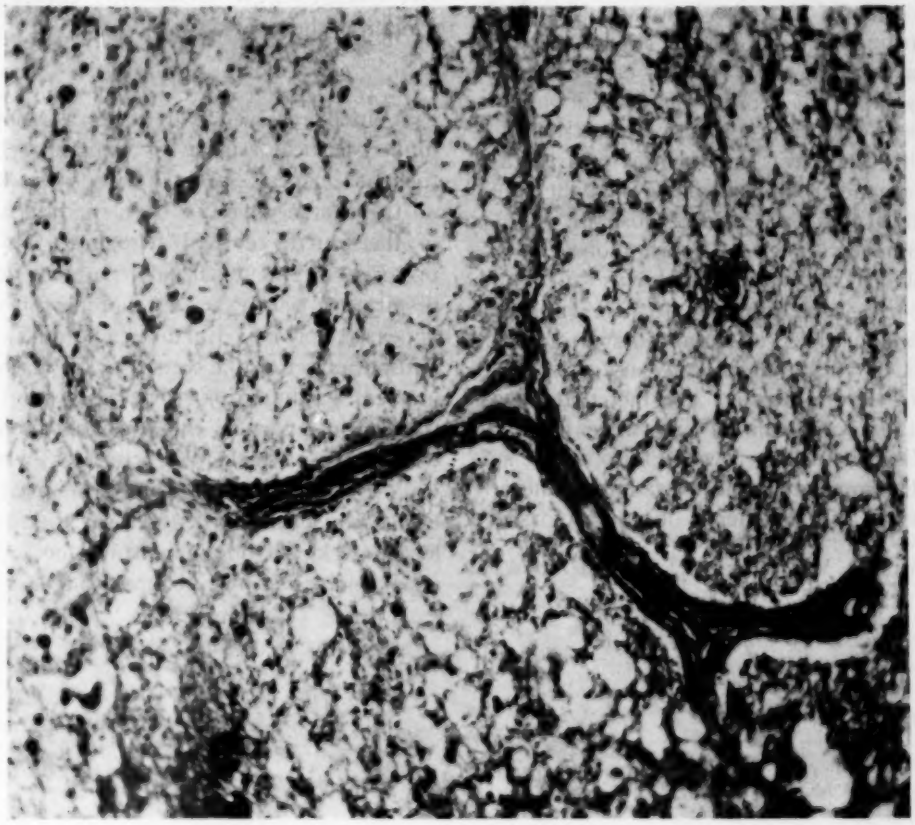


Fig. 2.—Small artery in the white matter with a greatly thickened fibrous wall and a narrowed lumen, surrounded by demyelinated areas. A few lymphocytes can be seen in the outer portion of the arterial wall.

COMMENT

Lyman, Kupalov and Scholz [3] demonstrated experimentally in dogs that roentgen rays have a profound effect on the central nervous system. It was their conclusion that this effect is not due to a primary effect on the neurons, but results from changes secondary to a profound vascular reaction consisting of hyaline degeneration and obliterating sclerosis of arterioles. Colwell and Russ [4] and Stafford Warren (Duggar [5]) likewise reached the same conclusion. Alpers and Pancoast,[6] however, did not observe thick-

3. Lyman, R. S.; Kupalov, P. S., and Scholz, W.: Arch. Neurol. & Psychiat. **29**:56, 1933.

4. Colwell, H. A., and Russ, S.: X-Ray and Radium Injuries: Prevention and Treatment, London, Oxford University Press, 1934.

5. Duggar, B. M.: Biological Effects of Radiation, New York, McGraw-Hill Book Company, Inc., 1936.

6. Alpers, B. J., and Pancoast, H. K.: Am. J. Cancer **17**:7, 1933.

ening of vessels in human brain tissue surrounding tumors which had been subjected to radiation. Smithers, Clarkson and Strong [7] described a case in which a lesion of the spinal cord developed one year and three months after the patient received therapy for a carcinoma of the upper third of the esophagus. A Brown-Séquard syndrome resulted from a unilateral lesion in the left side of the spinal cord at the level of the third and fourth thoracic segments. The lesion was intramedullary, and there was no sign of block in the spinal subarachnoid canal. It was postulated that the lesion could only be one of intramedullary gliosis, i. e., spinal gliosis, which may or may not be an early stage of syringomyelia. The cerebrospinal fluid was normal and the Wassermann reaction negative. The level of the lesion was in the previously irradiated region, and it was calculated that the spinal cord at this point received a dose of 5,800 r in thirty-nine days. No postmortem observations were available, since the patient was still living.

We are presenting our case because we believe that the lesion observed represents an unusual end result of radiation therapy not previously reported in the literature. The fact that metastases of the lymphoepithelioma were found in the vertebral bone marrow at autopsy is sufficient indication that intensive radiation therapy was necessary. When depth-dosage factors are taken into consideration, it may be calculated that our patient received from 6,000 to 8,000 r at the level of his spinal cord. It was the opinion at the time of admission that this amount of radiation could not have been responsible for the clinical appearance of this man on admission and the progress of his disease after admission. The fact that postmortem microscopic examination revealed degenerative changes of the spinal cord closely associated with thickened arteriolar walls warrants the conclusion that the degenerative changes were secondarily the result of the radiation therapy.

7. Smithers, D. W.; Clarkson, J. R., and Strong, J. A.: Am. J. Roentgenol. **49**:606, 1943.

SUMMARY

A man received intensive radiation therapy in the cervical region for lymphoepithelioma of the nasopharynx. About two years later signs of transverse myelitis developed in the region of the fourth cervical segment. This myelitis progressed and eventually led to death from respiratory paralysis. At laminectomy the cord appeared normal. Further radiation therapy was without effect on the course of the disease. Postmortem examination revealed myelomalacia of the cervical part of the cord, in the vicinity of which many thickened arterioles with fibrous walls could be seen. This is believed to be an unusual reaction to roentgen ray therapy directed to the neck, but one which must be kept in mind when such therapy is contemplated.

MEDIASTINAL TERATOMA

LIEUTENANT COLONEL SLOAN J. WILSON AND MAJOR REUBEN CARES
MEDICAL CORPS, ARMY OF THE UNITED STATES

Dermoid and teratomatous tumors of the mediastinum are relatively rare. Hertzler [1] in 1916 reviewed the literature as far back as 1825 and was able to find only 72 reported cases. Hedblom [2] in 1933 added 113 cases. Phemister, Steen and Volderauer [3] in a later survey to and including July 1936 stated that reports of 208 cases had been published, of which only 48 were cases of teratoma. Houghton [4] reported an instance of true teratoma of the mediastinum and found only 24 cases in the literature that he would accept as being cases of cancerous mediastinal or intrathoracic teratoma.

The literature from 1930 to the present date (June 1944) has been reviewed, and several other cases should be added to the aforementioned surveys. The following investigators have reported single cases of teratoma arising from the three germ layers: Hablützel [5]; de Castro and Parreira [6]; Moir [7]; Stanbury and Oille [8]; Wheatley [9]; Cooper and Henry [10]; Doran and Lester [11]; Becker [12]; van Joost and Kopp,[13] and Aguilar.[14] Two cases have been described by Cabot.[15] Harrington [16] reported 6 cases in which the tissue elements had arisen from all three germ layers. One of these cases is included in the review of Houghton.[4]

1. Hertzler, A. E.: Am. J. M. Sc. **152**:165, 1916.
2. Hedblom, C. A.: J. Thoracic Surg. **3**:22, 1933.
3. Phemister, D. B.; Steen, W. B. and Volderauer, J. C.: Am. J. Roentgenol. **36**:14, 1936.
4. Houghton, J. D.: Am. J. Path. **12**:349, 1936.
5. Hablützel, C.: Schweiz. med. Wchnschr. **63**:1308, 1933.
6. de Castro, J. R., and Parreira H.: An. de med. int. **3**:935, 1934.
7. Moir, P. J.: Brit. M. J. **1**:463, 1936.
8. Stanbury, W. S., and Oille, W. A.: J. Tech. Methods **16**:52, 1936.
9. Wheatley, G. M.: Am. J. Dis. Child. **54**:1057, 1937.
10. Cooper, D. A., and Henry, C. M.: Internat. Clin. **2**:253, 1939.
11. Doran, W. T., and Lester, C. W.: J. Thoracic Surg. **8**:309, 1939.
12. Becker, B. J. P.: South African M. J. **13**:659, 1939.
13. van Joost, C. R. N. F., and Kopp, J. G.: Geneesk. tijdschr. v. Nederl.-Indië **81**:969, 1941.
14. Aguilar, H. D.: Publ. d. centro de invest. tisiol. **4**:309, 1940.
15. Cabot, R. C.: New England J. Med. **211**:689, 1934: **224**:207, 1941.
16. Harrington, S. W.: J. Thoracic Surg. **7**:191, 1937.

The accounts of several unusual instances of teratoma have been published. Struthers [17] reported a case of teratoma of the thymic gland in an infant 5 months of age. The thymic duct was still present. Fox and Haspers [18] described 2 unusual teratomatous tumors of the anterior mediastinum, one from two germ layers at least, and the other containing tissue of both liposarcoma and rhabdomyosarcoma. Schenck [19] reported a congenital teratoma of the aorta in a stillborn infant. Somolinos [20] published an account of a teratoma of the pericardium arising from all three germ layers.

It is the purpose of this publication to report a case of cancerous teratoma of the mediastinum arising from all three germ layers.

REPORT OF A CASE

An enlisted man, white, aged 29, was admitted to a station hospital June 7, 1943, with a complaint of a hard, dry cough. The onset of the cough was about three weeks prior to admission. He had been coughing mostly at night, and the prone position seemed to aggravate and induce paroxysms. The patient had reported on sick call about three days after his symptoms were first noted. At that time a swelling of his neck was discovered. Shortly thereafter his collars were tight. The swelling in the neck, according to the patient, had not been progressive.

Examination revealed the skin to be smooth and elastic with a few lesions of acne on the posterior aspect of the chest. The face was florid. The neck revealed a mass in the left anterior cervical triangle, measuring about 10 by 6 cm., extending down substernally and also filling the suprasternal notch. The mass was soft, rubbery, without tenderness and movable. The trachea and the larynx were displaced 3 to 4 cm. to the right. The thyroid gland appeared to be buried beneath the mass. The veins of the neck were engorged. The veins of the left upper region of the chest and the left arm were widely dilated. The patient's temperature throughout his hospitalization ranged between 99 and 100 F.

A roentgenogram of the chest revealed a dense homogeneous mass occupying the entire upper mediastinum and extending into the neck. Its lower border was at the level of the ninth thoracic vertebra. It extended widely into the midlung fields bilaterally, and its outline was fairly smooth. The trachea was displaced to the

17. Struthers, R. R.: Canad. M. A. J. **26**:68, 1932.
18. Fox, J. P., and Haspers, C. A.: Am. J. Cancer **28**:273, 1936.
19. Schenck, B.: M. Rec. **144**:276, 1936.
20. Somolinos, G.: Arch. cardiol. y hemat. **17**:152, 1936.

right and compressed. Densities were present in the right cardiophrenic angle, which were interpreted as a pneumonic process or as atelectasis due to mucus.

On June 10, a lymph node in the left side of the neck was obtained for biopsy. The node was almost completely replaced by tumor tissue with the exception of a hemorrhagic pole seen grossly. Microscopically, this area contained a number of residual lymph follicles separated by proliferating trabeculae. Most of the normal nodal tissue had been replaced by neoplastic cells. These were arranged in sheets and broad cords of neoplastic cells measuring from 30 to 60 microns in diameter. The nuclei were highly vesicular, with a delicate nuclear membrane and a single or double stellate or spheroid nucleolus. The cytoplasm was moderately abundant, pale staining, granular and foamy, with occasional areas of distinct cell outlines. Frequent mitotic figures were present throughout, both regular and atypical forms. A number of tripolar figures were present. A diagnosis was made of lymphadenoma of the reticulum cell type. Biopsy specimens were forwarded to a histopathologic center. The opinion of the pathologist was that the neoplasm in the cervical lymph node was metastatic and was possibly representative of a metastatic teratoma of the testis. Slides were then forwarded to the curator of the Army Medical Museum, and the following report was received: "We believe that the tumor is metastatic in the cervical lymph node. It is too undifferentiated to permit speculation as to the primary site."

The patient was transferred to a general hospital. There were dilated veins over the upper portion of the sternum and in the left axillary and the left scapular region. Treatment with roentgen rays of high voltage was given over a period of seven weeks, totaling 32 exposures with a total of 3,525 r being delivered to the skin. During the early part of the therapy the mass regressed 2 cm. It then maintained its size. A new nodule appeared in the sternal notch, which became progressively larger. A short course of treatment with an unfiltered mixture of erysipelas toxin and Bacillus prodigiosus cultures (Coley's toxin) was given without any apparent beneficial result. Because of the failure to elicit further regression in the size of the tumor and because of the patient's desire to be nearer home, arrangements were made for transferring him to another general hospital. En route, the patient and his attendant missed a train connection. He was admitted to a general hospital in the city to rest and walked into the admitting room. Shortly after admission the patient became dyspneic and was given oxygen. No particular significance was attached to this phenomenon, as the patient's attendant stated that this had happened on several occasions. On this occasion, however, the patient became progressively worse, and death ensued.

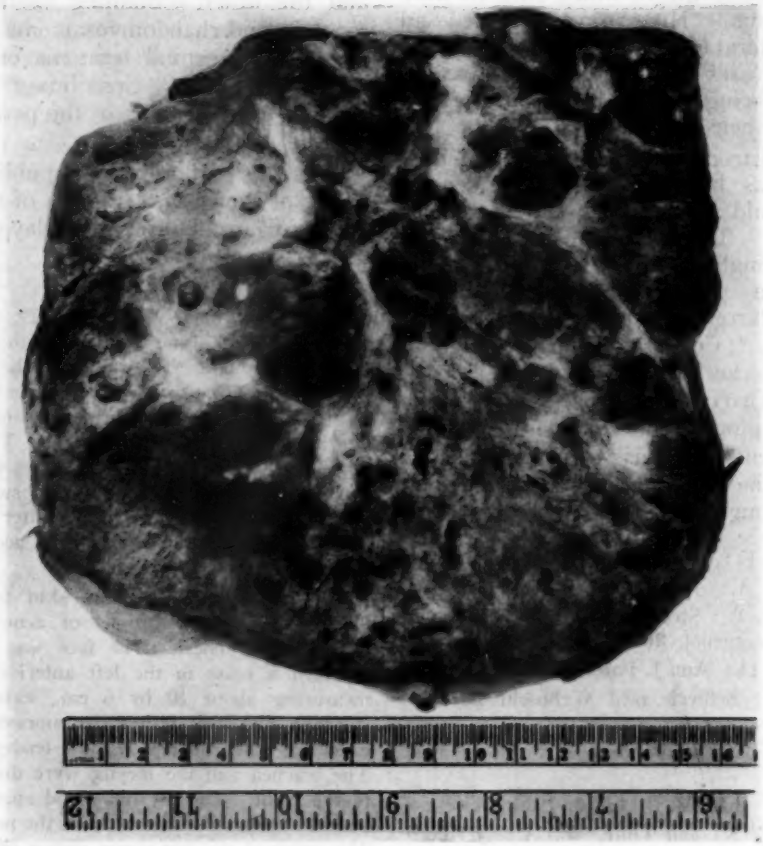


Fig. 1.—Photograph of the gross specimen showing the small cystic areas in many portions of the teratoma.

Autopsy.—The neck was markedly enlarged, particularly in the left supraclavicular region. The neck measured 17 cm. in width. The axillary and inguinal lymph nodes were palpable but small. The liver extended 7.5 cm. below the xiphoid process. There was about 300 cc. of clear straw-colored fluid in each pleural cavity. The superior mediastinum was wide and filled with a hard tumor mass. The mass extended down

over the pericardium and through the superior aperture of the thoracic cage into the lower portion of the neck, particularly on the left side. The pericardial sac contained about 200 cc. of clear straw-colored fluid. On removal the tumor mass measured 18.5 cm. in width, 17.5 cm. in its superior-inferior aspect and 9.6 cm. in thickness. It completely surrounded the ascending portion of the aorta and part of the arch. The trachea was not involved. The tracheal lymph nodes were only slightly enlarged. On cut section the tumor mass contained strands of what appeared to be fibrous tissue. Small cystic areas were scattered throughout. The tumor was hard, and alternate areas of pink and yellow were noted. Areas of hemorrhage were also present.

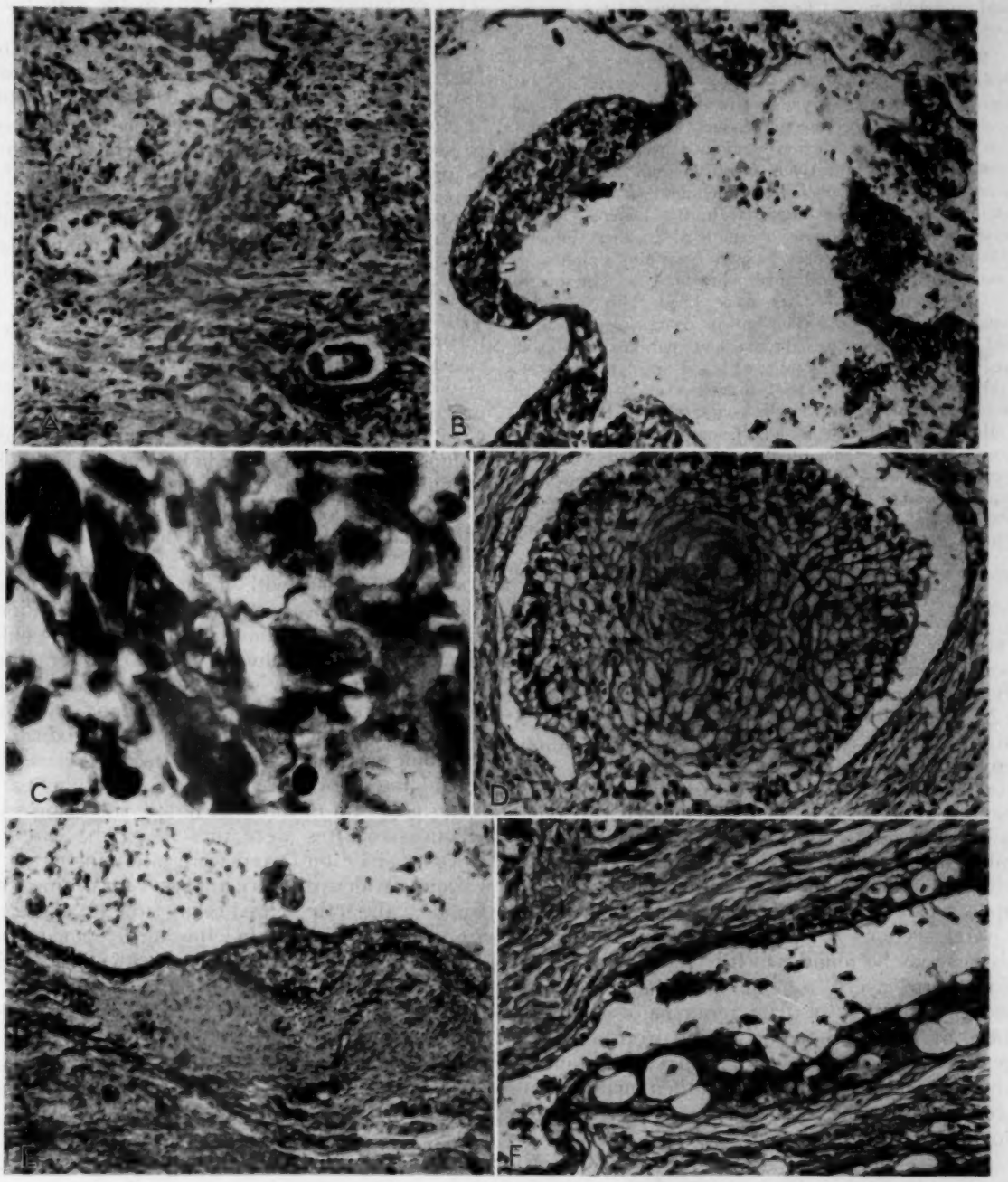


Fig. 2.—Photomicrographs of various tissue elements in the mediastinal teratoma. *A*, *B*, and *C*, choriocarcinomatous elements: *A*, tissue resembling endometrium with cytogenic stroma and glands in various stages of preservation. × 100. *B*, tissue resembling choriocarcinoma. The "villus" structure contains clear cells of the Langhans type. × 100. *C*, high power view of cells in *B*. Note the syncytial cells and others with paler cytoplasm and vesicular nuclei. × 400. *D*, *E* and *F*, other epithelial structures: *D*, clear cell pseudo pearl formation. Many solid clear cell nests scattered throughout the tumor resembled closely adrenal cortical tissue. × 120. *E*, metaplastic transition of clear cell epithelium such as that in *D* from a simple columnar type. × 90. *F*, hydropic degeneration in quasisquamous cyst lining. × 150.

The tumor showed no spread into either pleural cavity by direct extension. The neck was thoroughly dissected. The thyroid gland was not involved in the neoplastic process. No discrete lymph nodes were found. The entire tumor mass in the neck appeared to be an extension of the mediastinal neoplasm. The trachea was markedly compressed where it passed through the superior aperture. The lungs were thoroughly dissected, and no neoplasm was found. The testes did not contain any tumor masses.

Microscopic Examination.—The tumor was surrounded by a fibrous capsule. The matrix of the tumor was composed principally of myxomatous tissue and loose fibrous connective tissue. Scattered throughout almost every section examined were cysts lined with many different types of epithelium. Some cysts were lined with cuboidal epithelium, with an eosin-staining homogeneous material in the lumens. Other cysts contained little or no material in their lumens. The epithelial structures ranged from the simple columnar to the pseudostratified columnar type. In several of the sections the cysts were lined with stratified squamous epithelium. The lumens contained desquamated keratinized material; marked parakeratosis was also present. Cross sections of blood and lymph vessels were scattered throughout almost every section. In a few slides there were cells comparable to the cortical cells of the adrenal gland. Small areas of necrosis were scattered throughout. No extensive areas of hemorrhage were seen in any section examined. Tissue was present resembling endometrium with cytogenic stroma and glands in various stages of preservation. Other areas resembled choriocarcinoma.

COMMENT

There are many and varied classifications of teratoma of the mediastinum. Hedblom [2] described three types of teratoma: (1) epidermoid cyst containing only derivatives of ectoderm, (2) a dermoid type from ectoderm and mesoderm and (3) the true teratoma from all three embryonic layers. Askanazy [21] divided the true teratoma into two types: (1) the adult or cutaneous type and (2) the embryonal type, solid, of young growing tissues, with great inherent powers of proliferation. Harrington [16] observed that many mediastinal tumors may appear to be of the simple dermoid type, yet if careful sections of the wall are made, various tissues may be found which have arisen from all three germ layers. On this basis he objected to the classification of true teratoma as being a more or less solid tumor arising from all three germ layers and prefers to group all such tumors under the term "teratoma" and then qualify them according to the type of tissue which predominates.

The teratoma herein reported is the embryonal type, solid, and composed of young growing tissues in which there are cellular elements of a choriomatous type. At first glance the cellular structure of the metastatic lesion in the cervical lymph node appeared to be entirely different from the main tumor mass of the mediastinum. The metastatic lesion apparently was a proliferation from a single germ layer. In many respects it had the appearance of a metastasis from a seminoma of the testis, and this possibility was suggested by one of the pathologists reviewing the case. Figure *2 B* illustrates a villus which when examined under high magnification (fig. *2 C*) contained large pale cells of the Langhans type associated with masses suggestive of the syncytium noted in the metastatic lesion. The large pale glycogen-rich cells in the lymph node also resembled the chorionic cells of Langhans.

Numerous hypotheses have been formulated to explain the relationship of teratoma, particularly that of the testis and the ovary, and the appearance of choriocarcinomatous elements. Schlagenhaufer [22] advanced the theory that every choriocarcinoma arises from an embryonal teratomatoid element in which there is cancerous proliferation of an isolated blastomatous element with proliferation of fetal chorion. Ewing [23] recorded a number of testicular tumors giving rise to chorioma, in which several limited areas of syncytial cells were present, the origin of which was not clear. Hemorrhage is not necessarily a constant feature of choriocarcinoma. With such a tumor hemorrhages may be absent or negligible in multiple pulmonary metastases.

Little mention is made in the literature of choriomatous elements in mediastinal teratoma. Arendt [24] reported a case of gynecomastia in a 20 year old man with a mediastinal teratoma showing choriocarcinomatous transformation. Houghton [4] was of the opinion that there could be a hormonal stimulus of a quiescent teratoma of the mediastinum from hyperplasia of the normal interstitial testicular cells, such a stimulus inciting unrestricted neoplasia of reproductive chorionic elements. Becker [12] described elements resembling choriocarcinoma in the pulmonary metastases of a mediastinal teratoma. Chorionic villous structures were present in the case of Doran and Lester [11] and were intermingled with various tridermal structures. According to Budde,[25] the totipotential cells of the blastomeres are dissociated before the development of separate germ layers in those cases in which teratoma gives rise to choriocarcinoma.

SUMMARY

A solid teratoma of the mediastinum arose from all three germ layers in a white man aged 29 years. The teratoma contained choriocarcinomatous elements and had metastasized to a lymph node in the posterior triangle of the neck.

21. Askanazy, M., cited by Houghton.[4]

22. Schlagenhaufer, cited by Ewing.[23]

23. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1941.

24. Arendt, J.: Fortschr. a. d. Geb. d. Röntgenstrahlen **43**:728, 1931.

25. Budde, M.: Beitr. z. path. Anat. u. z. allg. Path. **68**:512, 1921.

General Reviews

ARTERIOSCLEROSIS

W. C. HUEPER, M.D.
NEW YORK

THE ANOXEMIA THEORY

(Continued from Page 65)

COLLOIDAL PLASMATIC DISTURBANCES: A. CARBOHYDRATIC TYPE

The anoxemic arteriosclerotogenic mechanism active in colloidal plasmatic disturbances differs fundamentally from that present in the vasotonic and the hydrostatic hypotensive and hypertensive disorders. The interference with vascular oxygenation here is not caused by stagnation or ischemia resulting from abnormalities in the speed of blood flow, the amount of blood supply and the pressure exerted by the vascular content on the vascular walls but is due to an impairment of the exchange of gases and other nutritive material through the interface between the blood and the vascular wall by the interposition of a film or a precipitate formed by some normally colloidally dispersed component of the plasma and causing subsequently a reduction in the permeability of the vascular walls. Such a disturbance in the colloidal equilibrium and stability of the plasma may be brought about by derangements in the quantitative relations or the physicochemical status of the normal colloidal constituents of the plasma (proteins, carbohydrates, lipoids) or by the appearance of abnormal endogenous colloids in the plasma (hypermacromolecular and hypomacromolecular serum proteins) or by the introduction of exogenous colloidal agents into the blood for therapeutic or experimental purposes (gelatin, ovalbumin, azoproteins, chemoallergic antibodies and antigens, heterogenic glycogen, polyvinyl alcohol, methyl cellulose, pectin, acacia [Hueper]). After injuring the endothelial lining through interference with its metabolic activity, these agents penetrate with the plasma into the intima and finally also into the media of the vascular wall and become an integral part of its structure by being deposited in the interstices and by being taken up into the cytoplasm of endothelial cells and histiocytes. In adjudging the morphologic appearance of the vascular changes elicited by these substances consideration must be given to the fact that colloidal lipoids and carbohydrates when taken up into the proteinic cytoplasmic matrix form a heterogenous emulsion giving rise to a foamy cytoplasmic structure. The inclusion of proteinic matter in the cells, on the other hand, results in the production of a homogenous emulsoid.

The concepts just developed presuppose that molecularly or micellarly dispersed colloidal substances are taken up by the endothelial cells of the vascular wall and penetrate into the vascular wall. The normal artery is permeable for water, salt solution, dextrose, bile pigments and hemoglobin. This permeability serves nutritional purposes. The degree of permeability fluctuates with the width of the vessel, the blood pressure and the temperature (Zettler; Lange and Donomal; Lange and Sebastian). Many vasoactive drugs, such as sodium nitrite, theobromine, sodium salicylate, theophylline, theophylline ethylenediamine, mersalyl and others, produce a definite and rapid increase in vascular permeability, while other drugs of this type, such as calcium chloride, calcium gluconate and nicotine, depress the permeability of the vascular wall.

Perfusion experiments on isolated pieces of arteries, as well as in vivo studies, have shown that highly dispersed colloidal dyes, such as fluorescein and naphthol yellow, diffuse into the vascular wall without changing the latter's status of contraction (Zettler). Petroff injected colloidal solutions of trypan blue and lithium carmine into rats and rabbits and found that these colloidal dyes penetrate first into the outer part of the media, then into the inner part and finally into the middle part, indicating that the dyes enter the vascular wall not only through the vasa vasorum but also from the vascular lumen by penetrating the intima. When vessels were rinsed with these vital dyes, only the inner part of the media and the inner elastic membrane became stained. Colloidally dispersed dyes present in the plasma thus enter the vascular wall in the course

From the Warner Institute for Therapeutic Research.

of the normal nutritive processes of these tissues. Dye solutions injected intravenously into rabbits previously given injections of epinephrine hydrochloride accumulate in the injured necrotic and calcified parts of the vascular walls, indicating that the penetration of injured tissues by colloidal material present in the plasma is accentuated. Okuneff confirmed these observations, using trypan blue, which he injected into cats and dogs. He found that the dye caused imbibition of the vascular wall and accumulated in sites where Anitschkow noted the localization of lipoid spots. The aortas of rabbits, guinea pigs, rats and mice, on the other hand, did not exhibit this focal distribution of the dye but showed diffuse imbibition. Glasunow then rinsed the aortas of rats, guinea pigs and rabbits with a solution of trypan blue and noted that after prolonged rinsing the posterior wall of the rat aorta was more intensely stained than the anterior aspect and that the orifices of the branches stood out because of their more pronounced staining. Boysen showed in experiments on rabbits with a Clark-Sandison window in the ear that india ink particles did not enter the endothelial cells of the capillaries, while trypan blue remained in the blood in a state of colloidal dispersion. Precipitation of the dye occurred only when the dye was taken up by perivascular histiocytes. The endothelial cells remained free from dye particles.

The reported experimental data provide definite proof that colloidally dispersed matter present in the plasma can enter the normal vascular wall. Since the causal role of colloidal plasmatic disturbances in the production of the atheromatous or the atherosclerotic type of arteriosclerosis can be most readily and convincingly demonstrated by the evidence obtained with exogenous macromolecular carbohydrates, as they are normally not present in the blood and after their introduction do not participate in any physiologic process, the experimental atheromatosis and atherosclerosis elicited by the parenteral introduction of these agents will be presented first.

Exogenous Disturbances.—Solutions of polyvinyl alcohol, methyl cellulose, pectin and acacia form emulsions with plasma. As these agents display distinct film-forming properties, they apparently coat the surface of the erythrocytes and thus interfere with the speed of oxygenation of these cells (Hueper; Martin and Hueper; Christie, Phatak and Olney). Their introduction into the blood elicits the hematic macromolecular syndrome, which includes increased sedimentation and pseudoagglutination of the erythrocytes and colloidoclastic leukopenia, as well as reticuloendothelial and parenchymatous thesauroses similar to those produced by cholesterol and other lipoids. While polyvinyl alcohol and methyl cellulose are relatively stable and chemically comparatively inert, acacia and particularly pectin are unstable and depolymerize in solution, especially on heating. In solutions of pectin this process apparently proceeds so rapidly and extensively on heating that autoclaved solutions of pectin do not give rise to atheromatous changes, as the pectin molecules have been broken down to molecules of such a small size as to permit their ready passage through biologic membranes. Macromolecular carbohydrates of the mentioned types which elicited atheromatous lesions had an average molecular weight ranging from 32,000 to 200,000. It may be pointed out that these substances form straight chain molecules (polyvinyl alcohol, methyl cellulose, pectin) or branched chain molecules (acacia).

Polyvinyl Alcohol Atheromatosis.—Experimental studies (Hueper; Hueper, Landsberg and Eskridge; Young, Mulay and Christie; Katzenstein, Winternitz and Meneely; Foster and Jenkins) on dogs, rabbits and rats given intravenous and intraperitoneal injections of aqueous solutions of polyvinyl alcohol have shown that this material is retained for prolonged periods in the blood plasma and is stored in various organs (in the reticuloendothelial cells and histiocytes of the liver, the spleen, the kidneys, the lungs, the pancreas, the heart, the intestine, the bone marrow, the adrenal glands and the lymph nodes, in the endothelial cells of the aorta and the pulmonary, renal, coronary, cerebral, carotid and femoral arteries and glomerular tufts and in the glia and ganglion cells of the brain).

Points of resemblance between cholesterosis and retention of polyvinyl alcohol (which may be termed polyvinylosis) are supplied by the following facts: Polyvinyl alcohol, just like cholesterol, is chemically a relatively inert substance which forms with the plasma a finely dispersed emulsion; paralleling the so-called protective qualities of cholesterol, based on the high resistance of this substance to enzymatic degradation and on its impermeability to many agents, polyvinyl alcohol displays comparatively marked chemical stability, refractoriness to the enzymes of normal tissues and impermeability to fats, oils, greases and gases. Because of its macromolecularity and the lack of adequate means of degradation, polyvinyl alcohol is retained in the blood over long periods and tends to coat the inside of the vessels and the surface of the erythrocytes with a film. This film is either the result of a coalescence of fine droplets of polyvinyl alcohol or is the product of a precipitation of this sub-

stance in the interface between the plasma and the intima, as the solubility of polyvinyl alcohol depends on concentration of salts and other physicochemical factors.

The formal genesis of the atheromatosis due to polyvinyl alcohol also follows closely the pattern displayed by that due to cholesterol. The endothelium of the elastic vessels takes up the foreign matter from the blood and is transformed thereby into large, swollen foam cells. Following the reactive proliferation of the damaged endothelial cells which result in the formation of more or less thick cushions of foam cells, and subsequent to the penetration of the media by the polyvinyl alcohol, foam cell endothelial histiocytes invade the inner part of the media. The accumulation of polyvinyl alcohol in the endothelial histiocytes and in the interstices of the media is followed by the appearance of small numbers of fatty granules in the endothelial foam cells and in the muscle cells of the media and in the polyvinyl alcohol infiltrating these parts of the vascular wall. While the fatty substances found in the endothelial lining may be derived from the blood, those present in the media are apparently the result of phanerosis and cellular decay. The affected, usually markedly loosened, parts of the media reveal muscular degeneration and hyalinization as well as disintegration of the elastic fibrils. In animals given moderate amounts of polyvinyl alcohol these changes are restricted to the inner third of the vascular wall. However, in animals with severe polyvinylosis there occur similar focal foam cell accumulations throughout the entire vascular wall, especially in the perivascular region of the vasa vasorum, which show under such conditions foam cell swelling of their endothelium also. The media of the organic muscular arteries often exhibits in addition to similar endothelial changes marked vacuolation of the muscle cells, the vacuoles being filled with globules of polyvinyl alcohol. It may be mentioned that the atheromatosis due to polyvinyl alcohol not infrequently affects the aortic leaflets by direct extension of the foam cell endothelial proliferation from the basal parts of the aorta upon the valves. Occasionally, a more or less thick coating of foam cells covers the inside of the left auricle and permeates its entire wall. Necrosis, hemorrhages and newly formed capillaries are found in some of the more abundant foam cell proliferations.

The atheromatosis induced with polyvinyl alcohol thus closely resembles in developmental as well as in morphologic respects the corresponding atheromatous change of the larger vessels and the lipoid degeneration of the media of the arterioles present in human atheromatosis. Its correspondence with the experimental cholesterol atheromatosis is equally close not only as to development and morphology but as to local distribution, since the ascending portion of the aorta of the animal given polyvinyl alcohol exhibits more marked atheromatous lesions than the abdominal part. On the other hand, the atheromatosis due to polyvinyl alcohol does not display the species-specific limitation possessed by experimental cholesterol atheromatosis. This distinction of the polyvinyl alcohol atheromatosis is evidently due to the fact that no species is provided with a metabolic mechanism capable of disintegrating this synthetic, foreign macromolecular material.

In contrast to cholesterol atheromatosis in man, the atheromatosis due to polyvinyl alcohol does not show any tendency toward calcification in lesions up to three months old. However, a calcifying type of polyvinyl alcohol atheromatosis can be elicited by combining parenteral administration of polyvinyl alcohol with oral ingestion of excessive amounts of vitamin D. Puppies 2 to 3 months old receiving 25 cc. of a 5 per cent solution of polyvinyl alcohol intravenously twice a week and 50,000 to 250,000 units of vitamin D daily by mouth until a total of 8 to 10 million units has been given during a period of fifty-five days show, in addition to extensive polyvinyl alcohol atheromatous lesions and scattered medial calcifications in the aorta, partially calcified atheromatous foci in the aorta, pancreatic artery and, most extensively, in the left auricle. The large platelike calcium incrustations of the thickened foam cell endocardium affect mainly the necrotic portions and are located in that part of the heart where the blood has a lowered carbon dioxide tension favoring the precipitation of calcium salts (Wells).

While these observations are of distinct importance from the standpoint of pathology, the information which they yield in regard to the causal genesis of atheromatosis and arteriosclerosis is of even greater significance. The data presented permit the conclusion that polyvinyl alcohol present in the blood as a finely dispersed emulsion and coating the vascular endothelial lining of the blood vessels interferes with the normal and adequate exchange of the various gaseous and liquid nutritive substances and waste metabolites between the blood and the inner third of the vascular walls. The resulting cellular injury is intensified when the polyvinyl alcohol is taken up by the endothelial cells and infiltrates the vascular wall, causing further clogging of the normal filtration membrane. The reactive

proliferation of the endothelial cells and their foam cell transformation produce atheromatous lesions. The physicochemical qualities of polyvinyl alcohol films toward fatty substances and the absence of any appreciable amount of fat-stainable material in these lesions, as well as of any hypercholesteremia, exclude any significant role of lipids in the development of these vascular changes.

Methyl Cellulose Atheromatosis.—Methyl cellulose, another highly polymerized carbohydrate, elicits when injected into dogs and rabbits hematic and organic reactions which closely resemble those produced by polyvinyl alcohol (Hueper; Hueper and Ichniowski; Katzenstein, Winternitz and Meneely). Like polyvinyl alcohol, it is a hydrophilic colloid with film-forming qualities which produces when introduced intraperitoneally or intravenously into the blood the hematic macromolecular syndrome and is retained there over long periods, forming an emulsion with the plasma. It is deposited in the reticuloendothelial cells and histiocytes of the lung, the heart, the liver, the spleen, the kidneys, the adrenal glands, the lymph nodes, the choroid plexus, the hypophysis and the small intestine, in the parenchymatous cells of the liver and in the endothelial cells of the elastic and muscular arteries and of the glomerular tufts.

The early vascular change usually consists of a focal foam cell transformation of the endothelial lining. This is sometimes preceded by a localized budlike or cushion-like proliferation of the endothelial cells. In some instances, just as in polyvinyl alcohol atheromatosis, the endothelial lining appears to be intact and an accumulation of foam cells is found beneath it, resting on the internal elastic membrane. In somewhat older intimal lesions there appears a proliferation of fibroblasts and of hyaline matter together with a decrease in the number of foam cells. With severe degrees of methylcellulosis, foam cells and free methyl cellulose–plasma emulsion penetrate the internal elastic membrane and invade the media. A foam cell transformation of the endothelium of the large vessels and foam cell accumulations around the vasa vasorum are then seen. Ultimately the entire vascular wall may be converted into a thick mass of foam cells under complete destruction of the media. Such changes occur particularly frequently in the myocardial and uterine arteries. Characteristic of the atheromatosis due to methyl cellulose is the appearance of focal and sometimes extensive hyalinizations and calcifications in the media beneath the foam cell intimal cushions. An isolated area of diffuse severe calcinosis of the media is occasionally seen in medium-sized muscular arteries without any intimal foam cell reactions being present. This type of arterial reaction resembles closely the Mönckeberg type of mediocalcinosis in man. Its occurrence under these circumstances indicates that colloidal plasmatic disturbances may play an important role in the production of such lesions.

The character of the vascular reactions elicited was identical regardless of the average molecular weight of the methyl cellulose used. Seven types of methyl cellulose were employed in the experiments, ranging in molecular weight from 32,000 to 140,000. These observations furnish another illustration suggesting that substances circulating in the blood and similar in physicochemical properties (chemical inertness, colloidal dispersion, nonpenetrability to nutritive and metabolic elements) are capable of producing atheromatous arterial lesions by impairing the oxygenation and nutrition of the vascular wall when deposited or precipitated on and in the vascular walls.

Pectin Atheromatosis.—Additional confirmation of this concept was obtained when solutions of pectin were injected into dogs and rabbits (Hueper). Pure citrus pectin, which has an average molecular weight of 200,000 and which consists of polymerized galacturonic acid molecules with various additional groups, elicits the hematic macromolecular syndrome and thesaurotic phenomena in the liver cells, the reticuloendothelial cells and histiocytes of the lungs, the liver, the spleen, the kidneys, the hypophysis, the choroid plexus and the bone marrow and in the endothelial cells and walls of the large and small arteries and of the glomerular tufts.

The primary vascular changes consist of small focal proliferations of the endothelial cells which stud the vascular lining like small seeds. These primary reactions grow to small elevated endothelial cushions which show a scanty accumulation of foamy cytoplasmic matter. Later larger cushions of foam cells appear which finally invade the media. This invasive response is associated with the appearance of large mononuclear cells within the cushions and in the media. There is a definite tendency of the larger cushions either to break down and ulcerate or to degenerate with disintegration of the foam cells, proliferation of fibroblasts and deposition of calcium salts. The final stage of this development is represented by hyaline and locally calcified thickenings of the intima. Hyaline degenerations of the media are found in the aorta, the pulmonary artery and the renal arteries.

These observations, which confirm those made in connection with polyvinyl alcohol atheromatosis and methyl cellulose atheromatosis, suggest,

moreover, that the speed with which degenerative, hyalinizing and calcifying changes occur in atheromatous lesions depends on the metabolic stability of the causal atheromatogenic substance.

Acacia Atheromatosis.—Acacia, another chemically complex, highly polymerized hydrophilic macromolecular carbohydrate, elicited when injected intravenously into dogs and rabbits a hematic macromolecular syndrome and storage reactions in the liver cells, the reticuloendothelial cells and histiocytes of the spleen, the lymph nodes, the kidneys, the adrenal glands and the lungs and in the endothelial cells of aorta and the glomerular tufts (Hueper). The foam cell intimal thickenings, however, were infrequent and small, while medial hyalinizations and calcifications were somewhat more frequent. The relatively moderate degree of the atheromatous responses observed in dogs and rabbits in spite of prolonged treatment with large amounts of acacia solution in high concentration is probably attributable to the instability of the macromolecules of acacia and the resulting fleeting nature of the disturbances in the colloidal plasmatic equilibrium. These observations are of clinical importance, as large amounts of acacia solution are injected intravenously into patients with nephrosis to counteract the existing hypoproteinemia, which is usually associated with hyperlipemia and hypercholesteremia, giving rise to atherosclerotic reactions.

Glycogenic Vascular Reactions.—In glycogen storage disease (von Gierke's disease), which is characterized by the hematic macromolecular syndrome and the deposition of glycogen in the liver, the heart, the kidneys and the brain, hyperglycogenemia is accompanied by hypercholesteremia (van Creveld; Wagner; von Gierke; Krakower; Beumer and Loeschke; Unshelm; Siegmund). Degenerative, sclerosing or atheromatous vascular lesions have not been observed in the relatively few cases of this disease, affecting mainly young children, which have come to autopsy. There are, however, several cases of this disease on record in which glycogen was found in unusual amounts in the endothelium and muscularis of small arteries (von Gierke; Kimmelstiel; Humphreis and Kato; Antopol, Heilbrunn and Tuchman; Hertz and Jecklen; Wolff). Hueper injected glycogen solution intravenously into 2 dogs daily for a period of thirty days and observed reactions of the blood conforming with the hematic macromolecular syndrome, focal edematous intimal swellings of the aorta and localized hyalinizations of the media of the aorta and some coronary and renal arteries. In view of the small number of animals used, the short duration of the experiment and the relatively small amounts of glycogen injected, the glycogenic origin of these moderate vascular reactions is merely suggestive.

Summary.—The observations recorded show that repeated intravenous or intraperitoneal injections of excessive doses of various highly polymerized macromolecular carbohydrates which are used or proposed for use as plasma substitutes elicit, in addition to colloidal plasmatic disturbances, atheromatous arterial reactions which are morphologically identical with those seen in man and produced in rabbits by the feeding of cholesterol. The similarity between these experimental carbohydratic atheromatoses and the lipoidal ones extends to the topographic distribution of the atheromatous reactions within the vascular tree, the physicochemical conditions of the plasma underlying them and their relation to the causal mechanism responsible for the development of mediocalcinosis. The hyaline-calcinotic intimal thickenings representing the cicatricial end results of the atheromatous changes, on the other hand, are indistinguishable morphologically from similar lesions originating on a different causal basis.

COLLOIDAL PLASMATIC DISTURBANCES:
A. CARBOHYDRATIC TYPE

Antopol, W.; Heilbrunn, J., and Tuchman, L. R.: Am. J. M. Sc. **188**:354, 1934.

Beumer, H.: Klin. Wchnschr. **16**:654, 1937; Verhandl. d. deutsch. path. Gesellsch. **31**:188, 1938.

Boysen, B.: Frankfurt. Ztschr. f. Path. **45**:487, 1933.

Christie, A.; Phatak, N. M., and Olney, M. B.: Proc. Soc. Exper. Biol. & Med. **32**:670, 1935.

van Creveld, S.: Klin. Wchnschr. **12**:529, 1933; Medicine **18**:1, 1939.

Foster, R. H. K., and Jenkins, L.: Arch. Path. **37**:279, 1944.

von Gierke, E.: Beitr. z. path. Anat. u. z. allg. Path. **99**:369, 1937.

Glasunow, M.: Virchows Arch. f. path. Anat. **261**:837, 1926.

Hueper, W. C.: Arch. Path. **28**:510, 1939; **31**:11, 1941; **33**:1 and 267, 1942; **34**:34, 1942; **36**:381, 1943; Am. J. Path. **18**:895, 1942; **20**:211, 1944.

——and Ichniowski, C. T.: J. Pharmacol. & Exper. Therap. **78**:282, 1943.

——Landsberg, J. W., and Eskridge, L. C.: ibid. **70**: 201, 1940.

Katzenstein, R.; Winternitz, M., and Meneely, J.: Yale J. Biol. & Med. **16**:561, 1944.

Kimmelstiel, P.: Beitr. z. path. Anat. u. z. allg. Path. **91**:1, 1933.

Krakower, C.: J. Pediat. **9**:728, 1936.

Martin, G. J., and Hueper, W. C.: Proc. Soc. Exper. Biol. & Med. **49**:452, 1942.

Okuneff, N.: Virchows Arch. f. path. Anat. **259**:685, 1926.

Petroff, J. R.: Beitr. z. path. Anat. u. z. allg. Path. **71**:115, 1922.

Siegmund, H.: Verhandl. d. deutsch. path. Gesellsch. **31**:150, 1938.

Wagner, R.: Ergebn. d. inn. Med. u. Kinderh. **53**:586, 1937.
Wolff, K.: Beitr. z. path. Anat. u. z. allg. Path. **97**: 289, 1936.
Young, W. R.; Mulay, A. S., and Christie, A.: J. Lab. & Clin. Med. **27**:1131, 1942.
Zettler, L.: Arch. f. exper. Path. u. Pharmakol. **185**: 141, 1937.

COLLOIDAL PLASMATIC DISTURBANCES: B. LIPOIDAL TYPE

Intimal lipoidal deposits, which in their pure form are represented by atherosis or atheromatosis and which appear in connection with fibrosing and hyalinizing processes as atherosclerosis, are the most frequent lesions of the large elastic arteries, but occur also in the larger muscular arteries (coronary, cerebral, pulmonary and renal arteries and, less often, splenic and mesenteric arteries and branches of the celiac axis) (Ophüls; Bork; Sappington and Horneff; Wolkoff; Versé). Arteries of the extremities contain, as a rule, only minor or moderate atheromatous lesions (Sappington and Horneff; Hesse; Kusnetzowski) unless special causal factors, such as diabetic hypercholesteremia, prevail (Hines and Barker; Sappington and Fisher). However, even under these conditions mediocalcinosis remains the characteristic lesion of the arteries of the lower extremities. The significance of atheromatous changes in the aorta and the coronary arteries is illustrated by a statement of Leary to the effect that practically all of the arteriosclerotic lesions of the aorta and the coronary arteries are of the fatty form. Haythorn, Taylor, Crago and Burrier mentioned, however, that during the advanced stage of aortic atherosclerosis there occurs overlapping of type lesions (atheromatous cysts, diffuse mediocalcinosis and plaque formation).

THEORIES AS TO THE ORIGIN AND ETIOLOGIC IMPORTANCE OF THE LIPOIDS IN THE ATHEROMA OF THE ARTERIAL INTIMA.—The role of cholesterol in the genesis of the intimal atheromatosis and of the intimal and medial calcinotic reactions often associated with the lipoidal reactions of the arteries and the origin of this substance have remained highly controversial subjects. Some (Virchow; Thomas; Faber; Lange; Staemmler; Moschcowitz; Beitzke) have asserted that cholesterol together with other fats is liberated in fibrous-hyaline intimal thickenings during the course of necrobiotic processes and thus represents merely a by-product of the regressive phase of intimal arteriosclerotic lesions. Beneke apparently held a similar opinion when he contended that intimal lipoidosis is the result of continued vascular tension or pressure. The presence of cholesterol deposits in the vascular lesions, according to the necrobiotic theory, is purely incidental. Many others (Aschoff; Ribbert; Marchand; Bürger and Schlomka; Lubarsch and others) have held that as a part of the colloidal aging process a loosening of the connective tissue ground substance of the intima precedes the appearance of cholesterol, which enters the altered intima together with the plasma from the vascular lumen and is retained there especially by the mucoid matter, which possesses a particular affinity for cholesterol (Schultz; Aschoff; Hueck; Saltykow; Stumpf; Torhorst; Voigt; Ssolowjew; Nordmeyer). This process of intimal imbibition of plasma with deposition of cholesterol is facilitated by hypercholesteremia. Hirsch and Weinhouse, and Landé and Sperry, again emphasizing the importance of primary changes in the intimal tissues for the precipitation of cholesterol, recently stated that cholesterol has no specific significance in the production of atheromatosis but acts indirectly through its influence on the physicochemical state of the plasmatic lipoids as a whole. The role of cholesterol in the production of atheromatous changes, according to Aschoff's theory of colloidal aging, is mainly a passive one, conditioned by primary colloidal senescing changes in the vascular wall.

Leary has recently modified this theory by claiming that cholesterol is introduced into the subendothelial tissue by cholesterol ester–containing lipophages that penetrate the intact endothelial lining. These cholesterol-carrying lipophages which are specifically attracted by the arterial intima are derived from desquamated foam-cellular reticuloendothelial cells of the liver, the adrenal glands and the lungs and show, according to Leary, all conceivable transitions between lymphocytes, large mononuclear cells and large lipophagic cells when circulating in the blood. Endothelial cells and intimal fibroblastic cells are primarily free from cholesterol. The alleged affinity of the vascular wall for these cholesterol ester–phagic cells is highly selective, as phagocytes containing other substances are not attracted by the arterial walls. Leary claimed further that in early youth the cholesterol esters are transferred from the lipophages to the proliferating fibroblasts in the intima, which undertake their metabolic destruction without the formation of collagen. In later life this quality of the fibroblasts is increasingly lost by the arteries except in the ascending part of the aorta. As there occurs then no proliferation of fibroblasts, the foam cells accumulate in the intima and give rise through necrobiotic disintegration to the formation of atheromas. Cholesterol assumes in this lipophagic theory a place secondary to the

specific "affinity of the vascular tissues, as it is the object of attraction," while the tissue reactivity is the important and variable factor, accounting for the different anatomic types of lesions characterizing various age periods.

A fourth theory was advanced several years ago by Winternitz, who asserted that the primary event in the evolution of an atheroma is represented by the penetration of newly formed capillaries extending either from the vascular lumen or from the vasa vasorum into the intima. Following the occurrence of hemorrhages from such intimal capillaries, cholesterol contained in the plasma and liberated from the disintegrating blood cells appears in the decomposing hemorrhagic foci and thus gives rise to the ultimate formation of necrotic intimal thickenings containing cholesterol and fat. The role of cholesterol in the formation of atheromas is evidently only a fortuitous one, according to this capillarization theory.

Anitschkow and his many followers (Beneke; Rosenthal; Cramer), on the other hand, maintained that the deposition of cholesterol in the arterial intima is the result of hypercholesteremia. The plasmatic cholesterosis leads in this theory to vascular changes (Koppenhöfer) as the cholesterol is taken up by the endothelial cells and subendothelial phagocytic cells, which are transformed thereby into foam cells, while at the same time the lipoid-containing plasma seeps into the interstices of the intima giving rise to accumulations of extracellular lipoidal material, especially along the internal elastic membrane, which acts as a filtration barrier for the plasmatogenic tissue juices. Quantitative fluctuations in the cholesterol content of the plasma, according to this hypercholesteremic theory, appear as the significant factor in the genesis of atheromatosis.

Hueper recently came forth with a new theory in which it was contended that the atheromatous process is initiated by an imbalance of the plasmatic colloid equilibrium causing the precipitation of a cholesterol film on the intima. Such a film, it was claimed, interferes with the proper exchange of gases and nutritive substances between the blood and the vascular wall, as cholesterol in a precipitated form is chemically relatively inert and impermeable to many substances. The resultant injury to the endothelial cells causes increased permeability of the endothelial lining and proliferation of the endothelial cells, which take up cholesterol and are thereby transformed into foam cells. A similar conversion into foam cells takes place in the intima where cholesterol contained in the plasmatic fluid penetrating into the subendothelial space is phagocytosed by histiocytes. The instability of the plasmatic colloidal solution of cholesterol which starts this chain of events in the vascular wall may be due to quantitative imbalance in the cholesterol content (hypercholesteremia), or it may result from an increase of substances in the plasma which decrease the dispersion of cholesterol and therefore favor its precipitation or from a decrease of substances which enhance the dispersion of cholesterol. The physicochemical properties of cholesterol decidedly influencing the oxygenation and nutrition of the vascular wall are significant factors in the production of cholesterol atheromatosis, according to Hueper's anoxemic theory, which is based on the analogous conditions present in the atheromatoses elicited by polyvinyl alcohol, methyl cellulose, pectin and acacia.

Inasmuch as the relative merits of the various theories cannot be properly evaluated without giving due consideration to normal and abnormal cholesterol metabolism, a brief résumé of the pertinent information on this subject is given first.

Cholesterol present in the blood and in the tissues is in part synthesized in the body; in part it originates from the animal food ingested, such especially as eggs, butter, milk, lard, brain and meat. Phytosterols contained in vegetable matter are not absorbed by the animal organism (Schönheimer and Yuasa; Schönheimer, von Behring and Humel; Schönheimer). Bloor stated that milk contains about 0.2 Gm. of cholesterol per liter, egg yolk about 1.9 Gm., and skeletal muscle 0.07 to 0.09 Gm. per kilogram. Hueck estimated that a baby when breast fed consumes daily about 49 to 97 mg. of cholesterol, and when on a mixed diet, about 62 mg. He estimated that adults on a fat-poor diet receive between 39 and 109 mg. daily, those on a mixed diet between 200 and 362 mg. and those on a high fat diet up to 1,400 mg. Milk contains cholesterol mainly in the form of esters, whereas meat and brain contain mostly free cholesterol. Cholesterol added in a dry form to food poor in fat is not absorbed by the intestinal mucosa. Foodstuffs rich in fat or oil, on the other hand, dissolve cholesterol, which is emulsified in the intestine through the action of bile acids, particularly by desoxycholic acid and its alkaline salts, less by taurocholic and glycocholic acid (Wieland and Sorge). In the absence of fatty acids, free and esterified cholesterol does not pass the intestinal mucosa. The lymph of the thoracic duct contains 25 to 30 per cent of the total cholesterol in the free form; the balance is in the ester form, bound to fatty acids (Bloor; Hueck) mainly of the unsaturated reactive type (Blood, Blake and Bullen). A similar ratio (2:1) of esterified cholesterol to free cholesterol is noted in the plasma, which normally contains from 130 to

230 mg. of cholesterol in 100 cc., while the bile contains from 39 to 61 per cent free cholesterol. Cholesterol is not readily degraded metabolically (Bürger and Schlomka) and is excreted with bile, sebum, milk, intestinal secretion and urine and through the skin, the lungs and the bronchi.

Both free and esterified cholesterol are anisotropic and occur in the plasma in colloidal dispersion (Bruger). The plasmatic cholesterol represents the bulk of the total blood cholesterol content as only relatively minor amounts of cholesterol are contained in leukocytes and erythrocytes. Since cholesterol is a hydrophobic colloid, it is held in colloidal dispersion by the presence of hydrophilic colloids (lecithin, protein) (Degwitz; Hirsch and Weinhouse). Remesow noted that the labile hydrophobic cholesterol mycelle can be converted into a hydrophilic one by the addition of protein, carbohydrate or fat. Cholesterol–plasma protein addition products occur in the plasma (Bennhold). The close physicochemical relations between these two substances are demonstrated, moreover, by the fact that 70 per cent of the total cholesterol is precipitated with the protein by the salting out method. Weinhouse pointed out that cholesterol is bound to albumin by secondary valences or is combined with it through opposite electrical charges holding protein micelles and high molecular aggregates of lipoid molecules together or becomes associated with protein by simple physical enmeshing. This attraction between cholesterol and protein aggregates results in a uniform dispersion of discrete lipoid molecules throughout the protein micelles. It is apparently for these reasons that Bruger found in ultrafiltration experiments on transudates and exudates that membranes which were not permeable to proteins did not permit the passage of cholesterol, indicating thereby that cholesterol exists in these plasma-like fluids in large molecular aggregates approximating the protein micelles in size and resembling them in other physical properties. The firmness of the binding of cholesterol to protein can be varied in vitro by the addition of small amounts of dextrose or salts to serum and appears to be changed after the intravenous injection of crystalloid solutions, according to Handovsky. While molecular cholesterol is chemically relatively nonreactive, colloidally dispersed cholesterol is chemically highly active, displaying strong reducing qualities and oxidase activity (Remesow).

Lipschitz, on the other hand, suggested that cholesterol may impair oxidative processes. Cholesterol, which in contrast to proteins and phosphatides has practically no electric charge, acts electrically as an insulating agent which inhibits the permeability of membranes and thus the movement of ions to a degree corresponding with the amount of cholesterol present in the interface. Wacker and Hueck pointed out that cholesterol esters accumulate at sites of high carbon dioxide tension and proposed that a relation exists between this process and the inhibition of oxidation. Observations made by Martin and Hueper on the reduced speed of oxygenation of the erythrocytes of hypercholesteremic rabbit's support this concept. The biologic activity of cholesterol thus depends in part on its effect on membranes (Thannhauser; Hueck; Epstein).

It may be mentioned in this connection that hypercholesteremic thesaurosis of the spleen results in the development of an anemia (Okey and Greaves; Member, Ehrlich and Bruger) which has apparently the same hyperplastic splenic genesis as that seen in other lipoidal and carbohydratic thesauroses of this organ (Hueper). The anemiogenic effect of cholesterosis, however, must be distinguished from the transitory reduction in erythrocytes associated with alimentary hyperlipemia and caused by the increased erythrocytic fragility and destruction elicited by the action of fatty acids and soaps (Johnson, Freeman, Longini and Loewy; Longini and Johnson; Dupee, Johnson, Marchello, Wilner and Freeman). The hyperlipemia often accompanying hypercholesteremia may accentuate, on the other hand, the development and the severity of the splenogenic anemia by increasing the rate of destruction of erythrocytes.

The stability of the colloidal cholesterol solution is highly important. It is influenced by the cholesterol-lecithin ratio (Medvei; Tannenberg; Hueck), the hydrogen ion concentration, the amount of albumin, the bile acids and other factors. While SS and SH groups in the protein molecules decrease the precipitability and increase the dispersion of cholesterol, NH_2 groups have an adverse effect on these conditions (Dirr). Kimmelstiel noted that the addition of galactosides to mixtures of cholesterol and cephalin or lecithin favors the precipitation of cholesterol. Addition of dextrose exerts a similar effect on cholesterol sols. An increase of cholesterol or other hydrophobic colloids therefore causes instability of the colloidal dispersion of cholesterol and its agglomeration into larger particles. This reaction is responsible for the appearance of opalescence in hypercholesteremic plasma. Free cholesterol reacts, moreover, with various toxins and hemolytic substances (saponins, digitonin), forming thereby addition products with lowered stability (Grigaut; Ransom; Ehrentheil and Weis-Osborn; Kollert; Lee and Tasi; Kyes and Sachs). Through its esterification with unsaturated fatty acids it may par-

ticipate in the metabolism and transport of these substances (Bloor; Hurxthal and Hunt).

Bürger found that the arterial blood contains regularly about 11 per cent more cholesterol than the venous blood and concluded therefrom that the blood lipoids undergo during their passage from the arterial to the venous side quantitative and qualitative changes. This observation agrees in principle with those made by several investigators concerning the arrest of cholesterol in the pulmonary capillaries, where cholesterol is temporarily kept and esterified (Remesow and Tavaststyerna; Abelous and Soula; Zinserling; Engel-Cserna; Kaufer). Remesow and Tavaststyerna, however, pointed out that apparently only the rabbit's lung metabolizes the arrested cholesterol injected intravenously, while the dog's lung treats it like a foreign body. This species-specific difference in the reactivity of the lungs of herbivorous and carnivorous animals may account for the fact that Shillito, Bidwell and Turner did not find any significant variation in the cholesterol content of the blood before and after passage through the lungs. Kovats noted that the blood coming from the spleen contained a higher fraction of esterified cholesterol than that in the blood going to this organ.

The validity of the necrobiosis theory of Virchow and others rests mainly on the observation that in marked fibrous and hyaline primary thickenings of the intima the development of necrotic processes is associated with the appearance of fat, including cholesterol, and of usually only a small number of foam cells. This fact, however, does not justify the conclusion that the majority of fat-containing intimal lesions are of this genesis. There are a large number of reliable observations attesting that the deposition of fat, usually together with some fibroblastic proliferation, is a primary reaction of the arterial intima. Chemical analyses of the fat content of atheromas have shown, moreover, that during the early stages of atheromatosis the lipid and lipoid composition of the atheromatous content (55 to 60 per cent esters; 23 to 26 per cent free cholesterol; 20 per cent other lipids) is similar to that of the blood. Among the various analyses made (Wells; Schönheimer; Kimmelstiel; Rosenthal; Page and Menschick; Lehnherr; Meeker and Jobling; Zeek; Landé and Sperry; Hirsch and Weinhouse; McArthur) those of Schönheimer, Hirsch and Weinhouse, Landé and Sperry, and McArthur revealed that the ratio of free cholesterol to esterified cholesterol in the atheromatous matter is about the same as that of the plasma, indicating the hematogenous origin of the lipoidal material. McArthur noted, moreover, that the fatty acids present in the esters are oleic, palmitic, linoleic and arachidonic acid and some other petroleum-insoluble unsaturated acids. The most striking difference between the fats in atheromas and those in normal tissue is in the neutral fats fraction, according to McArthur, as the fats of atheromas are 13 to 27 per cent neutral fats, whereas the proportion of these in the fats of normal plasma and blood cells is 35 to 41 per cent, suggesting that glycerides either are not absorbed from the plasma or undergo subsequent decomposition in the intima. The results reported by Hirsch and Weinhouse support the last-mentioned mechanism, as they found that the cholesterol content increases and the neutral fat and fatty acid contents drop sharply during a more advanced stage of the atheromatous development and undergo during the final stage a reversal of these quantitative relations.

The original colloidal aging theory of Aschoff does not take proper account of the fact that the chemical, physical and morphologic changes occurring in arteries with age are independent of atherosclerosis. The presence of lipoid spots in the aortic intima of babies and juvenile persons, moreover, demonstrates clearly that the changes of aging are not essential for the deposition of lipoids in the intima, while the rapidly increasing number of observations on the frequency of typical atherosclerosis, particularly of the coronary arteries, in young adults suffering from diseases accompanied by disturbances of the cholesterol content of the blood provide additional evidence against the validity of this theory. The experimental production of the so-called arcus senilis of the cornea resulting from the precipitation of cholesterol in this tissue and attributed by Aschoff to senile dehydration of the colloids has been accomplished in cholesterolized rabbits by Schönheimer, Versé, Kolen and Rosenthal. Joël, moreover, demonstrated the occurrence of arcus senilis in young and middle-aged adults having an increase in blood cholesterol but showing no evidence of premature senescence in any other organ. As the experimental arcus senilis is partly reversible, it is likely that any local tissue changes in the cornea are likely to be secondary and not primary and that the precipitation of cholesterol in this nonvascularized tissue, resembling in this respect the inner part of arteries, is based on physiologic conditions and not on pathologic ones. The arguments of Landé and Sperry and of Hirsch and Weinhouse in favor of unknown factors in the tissues of the blood vessels which allegedly favor the deposition of lipoids are based on the observation that the atherosclerotic lesions develop during adult life without any appreciable elevation of blood cholesterol or obvious abnormality of the blood lipids. It will be shown later in the discus-

sion of the various hypercholesteremic conditions that these contentions are not generally applicable since the evidence available on this matter does not support such generalizations. Hirsch and Weinhouse, as well as Kimmelstiel, concede, moreover, that the main cause of precipitation of the lipoid, in cholesterolized rabbits as well as in man with essential xanthomatosis may be of hypercholesteremic-hyperlipemic (cholesteatotic) origin and not related to any tissue factor of senile or undetermined nature.

The lipophagic theory of Leary is based on several assumptions and unconfirmed observations. One of the fundamental contentions of his theory deals with the presence of foam cell lipophages in the blood which are specifically attracted to the arterial wall. While it is possible that a few such cells circulate in the blood after being released from their normal sites in the spleen, the liver, the adrenal glands, and the lungs, there is no additional confirmatory evidence from any other source that these cells are of any significance in the production of atheromas, i.e., that they invade the subendothelial tissue by penetrating through an intact endothelial lining. This is an important fact weighing against Leary's theory in view of the huge amount of experimental work that has been done on the production of atheromatosis in rabbits and suggesting an incorrect interpretation of anatomic evidence. It is, moreover, not correct that the endothelial lining in experimental atheromatosis is intact, as it can readily be shown not only that foam cell accumulations are present beneath an apparently normal endothelium but that endothelial cells may become transformed into foam cells while the subendothelial tissue remains apparently intact (Hueper). Additional doubts as to the validity of this theory are derived from the fact that the foam cell reticuloendothelial proliferations accompanying several lipoidoses (Niemann-Pick disease, Gaucher's disease) do not give rise to atheromatous formations in spite of the fact that at least in Niemann-Pick disease foam cells containing anisotropic material are found in the circulating blood, which exhibits in some instances an elevated cholesterol level (Letterer; Zehnder; Hamperl; Baumann; Smetana; Tropp; Siegmund). The experiments of Hueper with polyvinyl alcohol, methyl cellulose, pectin and acacia have definitely shown that the alleged affinity of the arterial wall for foam cells is apparently not restricted to those containing cholesterol esters—assuming for the sake of argument that the concept of Leary concerning the hematic origin of the subendothelial foam cells is correct. The cited experiments of Hueper, as well as subsequent ones performed by him on rabbits fed cholesterol, have demonstrated, on the other hand, that the endothelial cells, as well as the subendothelial histiocytes, take up the atheromatogenic matter and become converted thereby into foam cells. The relatively low incidence of atheromatosis in the arteries of the lung, where, according to Leary, the foam cells are arrested and the cholesterol is metabolized, speaks against his theory.

The doctrine of Leary concerning the age-conditioned differences in the reactivity of the arterial wall to the cholesterol-containing lipophages is untenable on considering the fact that the same morphologic and topographic types of atheromatosis are observed in the young as in the old in connection with diabetes mellitus, chronic renal disease, essential xanthomatosis and other hypercholesteremic conditions. Whatever differences may exist in this respect between various age groups are attributable to other factors, such as static conditions, endocrinic function and the duration of exposure to the causal factors.

The teachings of Winternitz in his vascularization theory are based on the observation that the arterial wall is often quite vascular in and adjacent to the region of atheromatous plaques. It is in general recognized, however, that these capillary proliferations which extend from the vascular lumen and the vasa vasorum into the plaques are of secondary nature, appear only in advanced lesions and are not the cause of the plaque formation (Aschoff; Leary; Schlossman and Gerber; Horn and Finkelstein; Sumikawa; Goldmann; Paterson; Hueper). They are thought to be of reactive nature, intended perhaps for the better resorption and removal of the deposited lipidal or synthetic carbohydratic matter. In commenting on the theory of Winternitz, Scupham, de Takáts, Van Dellen and Beck pointed out the following two outstanding weaknesses of this theory:

> . . . The first difficulty is that, while the demonstration of anastomosing channels in the intima of normal arteries of different animal species can be accepted, it is a fact that the arteriosclerosis which occurs in such animals is most commonly medial, characterized by degeneration and calcification of this coat and not by atheromatosis, which is an important part of the lesion of simple intimal arteriosclerosis in man. The second difficulty is that these authors have failed to demonstrate anastomosing channels in the intima of the normal human aorta and arteries; yet it is in this very location that simple arteriosclerosis develops in man.

Hughes and Perry made special mention of the fact that in a case of marked intimal thickening of the aorta in a girl 7 weeks old vascularization was absent, while Horn and Finkelstein noted

that atherosclerosis of the pulmonary artery is relatively rare although the wall of the pulmonary artery is exceedingly vascularized. Peary, who studied the distribution of the vasa vasorum in the aorta, stated that atherosclerosis develops in the intima, i. e., in a region farthest removed from the vasa vasorum, although the richer the anastomosing network of the vasa in a given site, the greater is the likelihood that lesions will arise there. It may be pointed out in this connection that the vasa vasorum in the large veins penetrate to the intima (Schiefferdecker) but that atherosclerosis of these vessels is quite uncommon and seen only in the presence of severe and prolonged hypercholesteremia and after administration of large amounts of polyvinyl alcohol or methyl cellulose without any evidence of primary intimal vascularization complicated by intramural hemorrhage. Hemorrhages into atherosclerotic plaques have been observed repeatedly in man (Winternitz, Thomas and LeCompte; Wartman; Nelson; Paterson; Horn and Finkelstein; English and Finkelstein) together with the origin of intimal capillaries from the lumens of sclerotic arteries. The observations of Zinserling on organizing cardiac thrombi, on the other hand, showed that lipoid masses and foam cells appeared in the superficial parts of thrombi which were exposed to the surrounding blood and derived apparently from the infiltrating lipoid-containing plasma. The available evidence lends little support to the theory of Winternitz and mainly opposes it.

The hypercholesteremic theory of Anitschkow holds that cholesterol in the form of an emulsion with the lymph infiltrates the vascular wall and becomes adsorbed there to the ground substance and the surface of the elastic fibrils. For the development of the resulting atheromatous lesions it is not essential, according to the available clinical and experimental evidence, that the hypercholesteremia is persistent or that an appreciable increase in the blood cholesterol exists at all as long as there are factors active which cause precipitation of the cholesterol in the intima. Such factors of local type may be of physicochemical nature causing instability of the cholesterol sol, or they may be represented by a relatively slowed metabolism delaying the elimination of this substance, or they may appear in the form of an increased amount of ground substance accentuating the adsorption and retention of cholesterol. The cellular and fibrillar proliferative processes are regarded as secondary reactions to the presence of cholesterol (Anitschkow).

These concepts have not remained unchallenged. Thus Hirsch and Weinhouse noted that the specific significance of cholesterol in experimental atherosclerosis is uncertain, while the role of the increase of the other lipoids and their relation to cholesterol are equally obscure. Hypercholesteremia as the cause of atherosclerosis has not been demonstrated convincingly in man in the opinion of these investigators. Page, as well as Kimmelstiel, is equally skeptical in this respect and considers the importance of cholesterol in the genesis of atherosclerosis as much overemphasized and definitely uncertain. In view of these objections against the theory of Anitschkow it appears pertinent to review the relationship which exists between hypercholesteremia and atherosclerosis in man and experimental animals.

Endogenous Disturbances Associated with Hypercholesteremia and Instability of Plasmatic Colloidal Lipoids.—*Biliary Obstruction.*—Hypercholesteremia characterized by a relatively low cholesterol ester fraction (30 to 50 per cent of the total cholesterol) is associated with diseases causing obstruction of the bile ducts and thereby interfering with the elimination of cholesterol with the bile (Gardner; Hurxthal and Hunt; Stepp; Bürger and Habs; Epstein and Greenspan). The coexistence of chronic jaundice and xanthomatosis has been reported (Pye-Smith; Smith; Schulte; Murchison; Futcher; Moxon; Gull-Addison; Hertzler). Fagge recorded a case of chronic jaundice and multiple xanthoma of the skin and of the arteries (aorta and pulmonary artery), whereas Gabbe mentioned the occurrence of chronic hepatic disease, tuberous xanthomatosis, angina pectoris and coronary arteriosclerosis.

Essential Xanthomatosis. — Hypercholesteremia with predominance of the ester fraction accompanies familial essential tuberous xanthomatosis (Thannhauser; Bürger; Svendsen; Nékám and Ottenstein; Polano; Letterer; Müller; Gruenfeld and Seelig; Bloom, Kaufman and Stevens; Dauksys; Engelberg and Newman; Lane and Goodman). The coexistence of this type of xanthomatosis with cardiovascular diseases affecting often young persons and causing sudden death has been observed (Gwynne; Hess; Svendsen; Lane and Goodman; Lapowski; Lehzen and Knauss; Wise; Wolff; Muller; Engelberg and Newman; Bloom, Kaufman and Stevens; Fagge; Poensgen; Weidman and Boston; Chalatow; Weber; Arning; Montgomery; Thannhauser and Magendantz). In some of these cases the diagnosis of xanthoma endocardii was made. In others there were attacks of angina pectoris or there was hypertension related to atherosclerosis of the renal arteries (Engelberg and Newman). In some of these cases, as well as in additional ones, the post-

mortem examination showed extensive and not infrequently nodular atheromatous-xanthomatous intimal lesions in the large elastic and muscular arteries in the endocardium (Arning and Lippmann; Harbitz; Lubarsch; Bross; Schulte; Balzer; Hoffmeyer). It is characteristic of the vascular manifestations accompanying this lipoidosis that the atheromas are composed of masses of foam cells (vascular xanthomas) and that particularly the ascending part of the aorta and the coronary and pulmonary arteries are involved. The atheromatous changes noted in the pulmonary vessels resemble closely those seen in connection with pulmonary fibrosis caused by chronic empyema and caseous pneumonia, i. e., in conditions in which large amounts of lipoidal cytolytic material are liberated (Pagel; Fischer). The foam cell proliferations in the smaller arteries are sometimes so extensive that they occlude the vascular lumens, while they may narrow considerably the lumens of large arteries (Lehzen and Knauss). In such cases foam cells may penetrate through defects of the internal elastic membrane into the media. The vasa vasorum of such vessels are often involved by the same process. Degenerative changes in even large foam cell proliferations are rare. In old lesions there takes place a replacement of the foam cells by fibrous tissue such as is seen in ordinary atheromas.

Hypercholesteremia without a shift in the ratio of free cholesterol to cholesterol esters is found in many cases of Hand-Schüller-Christian xanthogranulomatosis (Eppinger; Bürger; Strong; Natali; Dauksys; Gross and Jacox). In several cases there was observed intimal lipoidosis of the renal arteries with atheromatous plaques in the aorta, which sometimes exhibited a xanthogranulomatous structure with foreign body giant cells and giant cells of the osteoclastic type (Natali; Heine; Chester; Hess and Schildhaus).

Diabetes Mellitus.—The disease, especially when not controlled by insulin, is often associated with a considerable increase in the cholesterol of the blood, which forms a part of the general hyperlipemia (Joslin; Warren; Hunt; Katsch and Krainick; Gibbs; Buckner and Bloor; Rabinowitch; Schöndorff; Strauss; Schuetz).

Diabetic hypercholesteremia, which is not infrequently accompanied by the appearance of xanthelasmas, is also associated with an increased incidence of atheromatosis affecting mainly the coronary arteries and those of the lower extremities. Rabinowitch stated that the usual time necessary for the development of arteriosclerosis in diabetes is five years. Diabetic arteriosclerosis develops within this period regardless of age (Rabinowitch, Richie and McKee). These investigators expressed the belief that an intimate relation exists between cardiovascular disease in diabetes and hypercholesteremia, which in their opinion is an important factor in the production of atherosclerosis in the young patient with diabetes. Hunt noted that arteriosclerosis develops prematurely even in juvenile diabetic patients and is increasingly important as a cause of death in adult ones. Similar observations were made in this respect by many others (Joslin; Warren; Gibbs, Buckner and Bloor; Schuetz; Strome and Blaine; Dublin and Lotka; Root, Bland, Gordon and White; Davis and Warren; Blotner; Strauss; White; Vander Veer; Pilgersdorfer; Lisa, Magiday, Galloway and Hart; Bell; Lisa, Magiday and Hart; Kauvar; Geiling; Dry and Hines). Dry and Hines estimated that the absolute incidence of arteriosclerosis to the degree of causing arterial insufficiency is much higher in diabetic than in nondiabetic patients (11:1). It is also known that an obliterating atherosclerotic process in the arteries of the legs which is usually more common in men than in women is much more frequent in diabetic women than in diabetic men, reversing the usual sex ratio (Dry and Hines; Collens and Wilensky). This apparent sex factor, however, may be related to the fact that diabetic women live longer than diabetic men.

It may be mentioned that atherosclerotic lesions of the aorta and of the coronary arteries have been found by Fisher, Dragstedt and Hueper in dogs surviving complete pancreatectomy by several months.

Hypothyroidism.—An additional source of hypercholesteremia exists in connection with hypothyroidism (cretinism, myxedema, athyreosis), affecting young and old persons alike (Gildea, Man and Peters; Bronstein; Gilligan, Volk, Davis and Blumgart; Heckscher; Mason, Hunt and Hurxthal; Gardner and Gainsborough; Greene; Hurxthal; Hurxthal and Simpson; Beutel; Fleischmann and Wilkins; Lerman; Means, Hertz and Lerman; Shelton; Wislicki; Zondek; Wilkins and Fleischmann; Wilkins, Fleischmann and Block; Thompson; Stokes; Fenz and Zell; Badwin, Michelson, Melnick and Gottfried). Similar observations were made in thyroidectomized animals (dogs, rabbits, rats) (Chaikoff, Entenman, Changus and Reichert; Fleischmann, Shumacker and Wilkins; Heckscher; Remónd, Columbiés and Bernardbeig; Juctschenko; Bollman and Flock; Thompson and Long; Onizawa; Messina; Fleischmann and Shumacker; Westra and Kunde; Sakurai;

Schmidt and Hughes). Craig, Lisser and Soley observed tuberous xanthomas in a case of extreme myxedematous hypercholesteremia. Duncan asserted that the hypercholesteremia usually present in persons with mental deterioration is the result of functional hypothyroidism caused by disuse of the thyroid gland. It may be noted in this connection that hyperfunction of the thyroid gland is associated with a low level of blood cholesterol (Schally).

Hurxthal found that the increase of serum cholesterol in hypothyroidism is not the result of lowered metabolism, as hypometabolic states of adrenal or pituitary derivation are not accompanied by hypercholesteremia. This conclusion is supported by an observation of Page and Farr, who reported that the hypercholesteremia associated with nephrosis was not affected when thyroid medication was given and thereby the low basal metabolic rate elevated. It must be mentioned that in myxedema hypercholesteremia and lowered basal metabolism are not the only abnormalities present. The minute volume is lowered, the circulation time is prolonged (Stewart and Evans; Wislicki), the number of erythrocytes is reduced (Thompson); the erythropoietic tissue is atrophied (Langhans), the plasma proteins and bicarbonates are increased, the excretion of calcium is decreased, the lipid phosphorus of the plasma is increased to the same extent as the cholesterol (Peters and Man) and the distribution of cholesterol between the tissues and the plasma is shifted in favor of the plasma, while the excretion of cholesterol is unaltered (Fleischmann and Wilkins).

The relation of these hypercholesteremic changes in hypothyroidism to the development and the incidence of atherosclerosis is established by the following observations: De Courcy noted that atherosclerosis is a frequent complication of myxedema. Falta mentioned the precocious occurrence of atherosclerosis in the adult form of myxedema. Black and Kampmeier reported that the correlation between arteriosclerosis and hypothyroid states was first described as early as 1888 and recorded several cases of hypothyroidism complicated by coronary arteriosclerosis. The occurrence of large atheromas in the aorta and in other arteries in cases of aplasia of the thyroid gland has been noted (Bourneville; Maresch; Marchand; Heyn and others; Rössle; Wegelin). Merkel reported in detail such a case with extensive arterial atheromatosis and calcinosis. Mason, Hunt and Hurxthal speculated on the basis of the hypercholesteremia observed in hypothyroidosis, stating that if arteriosclerosis is associated with abnormal retention of cholesterol together with decreased output of calcium one would expect a high incidence of arteriosclerosis in patients with myxedema and a lowered incidence in patients with hyperthyroidism. Wegelin often noted in endemic cretinism atherosclerosis of all degrees and called attention to the fact that atherosclerosis is frequent in those parts of Switzerland and Austria in which endemic goiter prevails. He concluded from this evidence that a severe reduction in the basal metabolic rate favors deposition of lipoid and calcium. Marine described a case of myxedema in which there was generalized atherosclerosis. Hoelzer saw extensive calcinosis preceded by lipoidosis of the muscular arteries in a 3 year old girl with congenital athyreosis. Isenschmid, as well as Wegelin, reported the occurrence of marked arteriosclerosis in cretins and attributed this to a metabolic cholesterol disturbance. Bruger and Rosenkrantz related the physiologic decrease of the thyroid activity and thus of the metabolism with age to the development of arteriosclerosis. However, as mentioned before, extensive investigations on the blood cholesterol level at various age periods have not shown any consistent elevations of this factor with advanced age.

These observations in man were confirmed by those made in animals. Von Eiselsberg obtained in goats and sheep after thyroidectomy severe aortic sclerosis and less considerable coronary arteriosclerosis. Similar observations were made by Pick and Pineles in 6 thyroidectomized goats, in which the sclerotic lesions affected the ascending part of the aorta, with calcinosis of the inner part of the media. Falta noted that hyperthyroidotic patients, on the other hand, rarely show atheromatosis, while Dungal reported that the inhabitants of Iceland, who have small, well functioning thyroid glands because of an adequate intake of iodine, show an unusually low rate of atherosclerosis of the large and small arteries.

Whereas the artificial production of hypothyroidism was accomplished in the past mainly by surgical or roentgenologic methods, recent studies have shown that this result can be obtained also by chemical means which interfere with the proper function and secretion of this gland, i. e., by prolonged medication with potassium iodide or iodotyrosine (Ghalioungui and Zell), by administration of thiourea compounds, thiobarbiturates, thiocyanides and sulfonamide compounds to man and animals and by feeding cabbage leaves or Brassica seeds containing cyanides to rabbits (Astwood; Mackenzie and Mackenzie; Mackenzie, Mackenzie and McCollum; Richter and Clisby; Kennedy; Astwood, Sullivan, Bissell and Tyslowitz; Blum; Whitehead, and many others). Detailed studies as to the effect of such medication over prolonged periods on the choles-

terol metabolism and on the vascular system are still outstanding but seem to be important in connection with aviation medicine and the therapy of hyperthyroidism.

Chronic Renal Disease.—Hypercholesteremia is a frequent hematic reaction in chronic renal disease characterized by degenerative processes of the tubules. The rise in blood cholesterol accompanying nephrosis may reach high figures (1,400 mg. per hundred cubic centimeters); there is a particularly marked increase of the ester fraction as well as of phosphatides and fatty acids (Petersilie; Löwenthal; Lichtenstein and Epstein; Gainsborough; Knauer; Blackman; Gilbert; Volhard; Calvin and Goldberg; Cook). It is usually combined with severe hypoproteinemia (absolute hypalbuminemia, relative hyperglobulinemia). Löwenthal, Rosenthal and Gilbert have described the occurrence of minor to extensive atheromatosis in the aorta and coronary arteries in 6 patients with lipoid nephrosis ranging in age from 4 to 29 years. Similar observations were made by others (Bing and Heckscher; Murphy and Warfield; Mason; Oppenheimer and Fishberg). Identical hematic lipoidal conditions prevail not infrequently in chronic glomerulonephritis with a nephrotic component. The hypercholesteremia here may also reach considerable values (Volhard; Steiner and Domanski; Epstein; Page, Kirby and Van Slyke; Lichtenstein and Epstein; Fahr; Redfield; Clark; Lauritzen; Chauffard, Laroche and Grigaut; Peters and Man, and many others), but xanthomatous manifestations are exceptional (Geyer). Inasmuch as chronic renal disease, like hypothyroidism, is often also associated with a disturbance of calcium metabolism, the atheromatous and atherosclerotic reactions observed in these conditions not only may be combined with those of the vasotonic and hydrostatic types but may sometimes show extensive intimal and medial calcification. Age factors are not involved in the production of these lesions, as chronic renal diseases represent the most frequent source of arteriosclerosis in childhood (Volhard; Ophüls; Addis and Oliver). Epstein pointed out that the basal metabolic rate is often low in patients with nephritic lipemia, but there does not exist a consistent relation between these two factors. It has been found, however, that in nephrotic lipemia the degree of hypercholesteremia exhibits an inverse relation to the degree of hypoproteinemia.

Exogenous Disturbances.—The effects on the vascular system of the hyperlipemia and hypercholesteremia seen after starvation as the result of the mobilization of body fat, after severe hemorrhage (Katsch; De Langen), after introduction of barbiturates, after anesthesia, in chronic benzine poisoning in man and rabbits (Nikulin and Hetmann), in chronic thallium poisoning (Klopstock), in anemia due to phenylhydrazine and hydroxylamine (Rosenthal and Meier; De Langen; Boggs and Morris; Morawitz and Pratt; Sakai) and in connection with chronic benzine poisoning in man and rabbits (Gaté, Chanial, Vallet and Humbert; Grütz; Wise) are unknown. Okuneff reported only the presence of lipoidal material in the endothelial cells and the intima of the splenic follicular arteries of starved rabbits. It may be mentioned in this connection that certain types of chemical poisoning elicit prolonged hypercholesteremia. Thus Bang saw in dogs and particularly in rabbits an increase of the blood cholesterol after phosphorus poisoning. Ssokoloff observed only a minor increase of blood cholesterol in rabbits poisoned with arsenic or phosphorus. A similar effect was elicited by injected diphtheria toxin. Strauss and Scheer reported a rise of cholesterol in the blood (up to 400 to 900 mg. per hundred cubic centimeters) in connection with vascular disturbances in heavy smokers. In animals exposed to nicotine over long periods the blood cholesterol level moved in an opposite direction from the iodine level, which was elevated in some animals and lowered in others, while the thyroid gland showed in some cases a hyperplastic condition and in others an atrophic myxedematous state. These observations suggest that in chronic nicotinism a cholesterogenic atheromatous factor may complicate the primary vasospastic action of the alkaloid.

Carbon Disulfide and Hydrogen Sulfide Poisoning.—Audo-Gianotti, Bianchi and Lewey noted in viscose workers exposed occupationally to the inhalation of carbon disulfide and hydrogen sulfide vapors a type of lipemia characterized mainly by an increase of free cholesterol and phosphatides. It is not known whether or not this lipemic reaction is of cytolytic origin and attributable to the destruction of nervous substance of the brain commonly seen in poisoning of this type. The workers had in addition to mental and neurogenic manifestations an unusually high incidence of cardiovascular disturbances, including angina pectoris (Gallego; Gordy and Trumper; Lewey). Audo-Gianotti noted the presence of vascular changes in viscose workers, which he attributed to the action of the "sulfmethemoglobin" formed. Arteriosclerotic lesions of the peripheral and retinal arteries of such patients were reported by Lewey and McDonald. The cerebral arteries of man, dogs and cats poisoned with carbon disulfide were observed to contain marked sclerotic changes (Lewey;

Alpers; Ferraro, Jervis and Flicker). Lewey attributed the vascular lesions to the increased incidence of hypertension among young viscose workers exposed to carbon disulfide and discounted any causal role of the hypercholesteremia in this respect.

Saponin Poisoning.—The parenteral introduction of saponins results in the development of an apparently cytolytic type of hypercholesteremia lasting up to twelve days after the injection (Kollert and Grill; Kollert, Kofler and Susani; Kollert and Rezek; Handovsky; Handovsky and von Trossel; Lasch; Ehrenteil and Weiss-Ostborn). Saponins cause, moreover, a disturbance in the colloidal lipoid equilibrium of the plasma, which influences the molecular dispersion of cholesterol (Ehrentheil and Weiss-Ostborn) and thereby the colloidal stability of the plasma (Lasch; Sobotka). This effect is due in part to the binding of cholesterol by saponin (Wacker and Hueck; Kofler and Fischer; Bayer and Gaisböck). Pachorukow reported the presence of jelly-like or fibrous nodular deposits firmly attached to the cardiac valvular leaflets (saponin endocarditis of Kobert) in animals given intravenous injections of saponin. Handovsky attributed the development of "arteriosclerotic" cholesterol deposits in the aortic intima of rabbits given saponin intravenously to the altered distribution of cholesterol in the plasma.

Physical Labor.—Severe and persistent physical labor elicits a hypercholesteremic reaction (Knack; Picard). Wacker and Hueck suggested that the prevalence of atherosclerosis in males might be attributable to this factor. It is doubtful, however, whether the manual labor of the male accounts to any appreciable degree for the definite difference in morbidity and mortality from atherosclerosis between the two sexes (Leary). It is more probable that a factor related to a sex hormone plays a role in this respect by preventing the deposition of cholesterol in the arterial walls. The existence of such relations is suggested by the fact that the hypercholesteremia accompanying pregnancy (Gruenfeld and Seelig; Katsch; Saito; Gardner) does not favor the development of atherosclerotic lesions but leads merely to the appearance of transitory lipoid spots (pregnancy spots) in the aortic intima (Popken). After parturition the cholesterol level of the maternal blood drops sharply, the excess cholesterol being apparently excreted with the milk (Knauer).

(To Be Concluded)

Notes and News

Grants in Aid.—Applications to the Committee for Research in Problems of Sex of the National Research Council for financial aid during the fiscal year beginning on July 1, in support of work on fundamental problems of sex and reproduction, should be received before April 1. They may be addressed to the chairman, Dr. Robert M. Yerkes, Yale School of Medicine, New Haven 11, Conn. Although hormonal investigations continue to command the interest and support of the committee, preference, in accordance with current policy, will ordinarily be given to proposals for an investigation of neurologic, psychobiologic and behavioral problems of sex and reproduction.

The Ella Sachs Plotz Foundation announces that grants will be given in aid of research in the sciences closely related to medicine. As a rule, the maximum amount granted is less than $500. Applications for grants to be held during the year 1945-1946 must be in the hands of the executive committee before April 1945. They should be sent to Dr. Joseph C. Aub, Massachusetts General Hospital, Fruit Street, Boston 14. There are no formal application blanks, but letters asking for aid must describe accurately the qualifications of the investigator and the research, name the amount requested and state whether other requests for support have been made.

Appointment.—Daniel Fowler Cappell, professor of pathology at the University of St. Andrews, has been appointed to the chair of pathology at the University of Glasgow, Scotland, in succession to the late Shaw Dunn.

Deaths.—Sir Joseph Arkwright, long connected with the Lister Institute, London, England, died Nov. 22, 1944, in his eighty-first year. He made important contributions to the knowledge of carriers of infectious diseases and to that of trench fever and typhus, of bacterial variation and of certain animal diseases.

Society News.—The annual meeting of the American Association for Cancer Research will be held at Cleveland, Monday and Tuesday, May 7 and 8, 1945, preceding the meetings of the Federation of American Societies for Experimental Biology. Dr. Lawrence A. Pomeroy, 952 Hanna Building, Cleveland, is in charge of arrangements. It is tentatively announced that the Hotel Cleveland will be the headquarters.

The Society of American Bacteriologists will meet at the Book-Cadillac Hotel, Detroit, May 22 to 25, 1945, under the presidency of I. L. Baldwin. The secretary is L. W. Parr, Washington University, Washington, D. C.

The Federation of American Societies for Experimental Biology will meet in Cleveland, May 7 to 10, inclusive, 1945.

The Toledo Hospital Institute of Medical Research, Toledo, Ohio, has received a grant of $13,000 from the Snyder Ophthalmic Foundation for research on the physiology of the eye especially in relation to glaucoma. The grant will be extended depending on the results obtained in the first two years. Because of the war, research will be delayed until a physiologist with specialized training in the eye become available.

Correspondence

IMPORTANCE OF TITLES THAT ACCURATELY REFLECT THE SUBJECTS OF THE ARTICLES

To the Editor:—In the December 1944 issue of the ARCHIVES OF PATHOLOGY there appeared an article by Albert E. Casey and Eleanor H. Hidden entitled "Nondevelopment of the Septum Transversum," in which they described a major defect in the diaphragm of a newborn infant who lived only four hours.

Autopsy showed absence of the central tendon and anterior portion of the diaphragm with the presence of a *pericardioperitoneal* foramen.

In the summary given in this paper it is stated "This is the first instance of this combination of anomalies to be recorded in the literature." They offer the case as proof of the embryologic concept that the septum transversum is "the anlage of the central tendon of the diaphragm, the ventrocaudal portion of the pericardium and the suspensory ligament of the liver."

Further, in the comment they mention Giffin's [1] review of the literature on diaphragmatic hernia (1912), in which he said that herniation into the pericardial sac had been reported but that he was unable to find the original description of the case and so could not state whether there was a direct or an indirect communication between the pericardial and the peritoneal cavity.

Casey and Hidden also refer to three papers by Hedbloom (1925, 1931 and 1934). In Hedbloom's first paper,[2] which contains an analysis of 378 cases in which diaphragmatic hernia was treated surgically, only 1 case is listed as a case of pericardial hernia, but it is not described nor is a reference given. In his last two papers Hedbloom made no note of pericardial hernia, and a personal communication from Hedbloom to Casey and Hidden indicated that he had not encountered a hernia extending into the pericardial sac in more than 400 cases in which he had operated for diaphragmatic hernia.

Finally, after a personal communication from Giffin, Casey and Hidden state that "Other than Giffin's and Hedbloom's mention of a diaphragmatic hernia extending into the pericardial sac no references to such an anomaly could be found in the literature. Since Hedbloom in his final report makes no reference to diaphragmatic herniation into the pericardial sac, his original mention probably referred to the defect cited by Giffin. Giffin has in his notes no reference to a direct communication between the pericardial and peritoneal cavities and states that since an original article describing such a case cannot be found, we are warranted in considering ours [Casey and Hidden] the first to be reported."

In order to set the records straight, I wish to state that in 1909 I reported a case in which there was a direct communication between the peritoneal and pericardial cavities and herniation of the transverse colon and great omentum into the pericardial sac.[3] This case, published under the title "A Case of Congenital False Diaphragmatic Hernia," is probably the one that Giffin had not been able to find.

The defect in this case was attributed to arrested development of the septum transversum and seemed to be of the nature of a teratologic rather than an embryologic fault and one closely allied to a beginning subthoracic ectopia cordis.

This anomaly occurred in a white man, aged 70, who had never had any serious illness throughout his life and had suffered no traumatism to his chest or abdomen. He was admitted to the hospital markedly cyanotic and dyspneic and lived seventeen hours.. The clinical diagnosis was congestive heart failure.

Autopsy showed a large defect in the central portion of the diaphragm, 6 cm. in diameter, through which the hand could be passed directly into the pericardial cavity. The distended transverse colon and most of the great omentum was virtually wrapped about the heart, causing an asphyxial type of death. Chronic adhesive peritonitis over several loops of small intestine suggested that such portions had at times herniated into the pericardial sac. There were no other anomalies.

I reported the case on account of its great rarity, as I was unable to find mention of any similar case in the literature. It was also of interest because of the age which the man reached with such a major defect.

Since this report I have never come across any reference to any similar case in the many articles which have appeared on diaphragmatic hernia.

The purpose of this communication is to emphasize the importance of the careful selection of titles for all medical articles. Many important papers and original observations are virtually lost in the enormous literature because the titles are not sufficiently descriptive. For instance, the title of my paper, "A Case of Congenital False Diaphragmatic Hernia," gives no indication of the presence of herniation into the pericardial cavity, which was the main reason for publication. With such a title it is impossible to give a paper proper classification in an index. Thus under the title quoted the article would be regarded by many workers as just another report of the ordinary, commonly recognized diaphragmatic hernia.

HARRISON S. MARTLAND, M.D., Newark, N. J.

1. Giffin, H. Z.: Ann. Surg. **55**:388, 1912.
2. Hedbloom, C. A.: J. A. M. A. **85**:947, 1925.
3. Martland, H. S.: Paper read at meeting of the New York Pathological Society, Jan. 13, 1909; J. A. M. A. **52**:1574, 1909.